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(71) Applicant *(for all designated States except US)*: **VIVANT MEDICAL, INC.** [US/US]; 3210B Alpine Road, Portola Valley, CA 94028 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BUCK, Richard, A.** [US/US]; 22491 Taranto, Laguna Hills, CA 92653 (US). **BUSH, Elisabeth, M.** [US/US]; 2068 Mento Drive, Fremont, CA 94539 (US). **FAWZI, Natalie, V.** [US/US]; 14 Somerset Court, Belmont, CA 94002 (US). **HOOD, Larry, L.** [US/US]; 25652 Nottingham Court, Laguna Hills, CA 92563 (US). **LEBOVIC, Gail, S.** [US/US]; 1204 Sharon Park Drive, Menlo Park, CA 94025 (US). **SIRIMANNE, D., Laksen** [LK/US]; 111 El Carmelo Avenue, Palo Alto, CA 94306 (US). **SUTTON, Douglas, S.** [US/US]; 1595 Adobe Drive, Pacifica, CA 94044 (US). **WALBRINK, Harold, J.** [US/US]; 58 Coronado Point, Laguna Niguel, CA 92677 (US). **POPE, Kerry, R.** [US/US]; 10231 Bubb Road, Cupertino, CA 95014 (US). **MORRISSEY, Anne** [US/US]; 570 Barron Street, Menlo Park, CA 94025 (US). **MOORMAN, Jack, W.** [US/US]; 136 Pinta Court, Los Gatos, CA 95030 (US). **WILSON, Peter, M.** [US/US]; 1105 Emerald Bay Lane, Foster City, CA 94404 (US).

(74) Agents: **BAGADE, Sanjay, S.** et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

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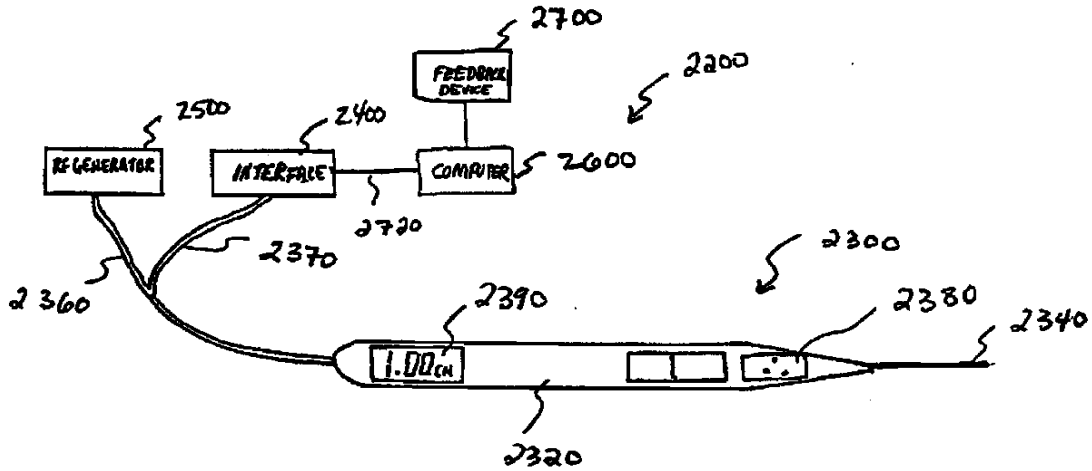

(57) Abstract: This invention is a tissue modification apparatus, method for accurately marking, and locating a lesion or other suspect tissue. More particularly, a tissue modification device (2300) such as a surgical cutter (2340) adapted with at least one proximity sensor (2380) for detecting the location, distance of a remotely detectable marker (2100), and a method for using the same, is disclosed. This invention also variously comprises a remotely detectable marker (2100), a control system (2600), a computer-readable medium, and feedback apparatus (2700) such as a visual display (2390). In operation, once the remotely detectable marker is deployed in the tissue of interest, the tissue modification device is used to modify tissue while determining the instantaneous location of the marker in space, and the instantaneous distance of the marker relative to a sensor (2380) to guide the cutting device (2340) to the marker (2100).

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DEVICE AND METHOD FOR SAFE LOCATION AND MARKING OF A CAVITY AND SENTINEL LYMPH NODES

FIELD OF THE INVENTION

This invention is directed to marking and/or locating sites within the body for the assessment and/or removal of cancerous cells and tissue. This invention is directed to methods and devices for marking and locating a lesion or other tissue abnormality within a mass of tissue. More particularly, this invention preferably utilizes a remotely detectable marker, a tissue manipulation device adapted to detect the marker, a computer-readable medium and a feedback device to enable one to accurately locate the position of the marker which has been placed in close proximity to the lesion or tissue mass of interest. This invention is also directed to subcutaneous cavity and sentinel node marking devices, delivery devices, and methods. More particularly, a cavity marking device, delivery device, and method are disclosed that enable one to determine the location, orientation, and/or periphery of the cavity by radiographic, mammographic, echographic, or other noninvasive techniques. The cavity marking device typically is made up of one or more resilient bodies and a radiopaque or echogenic marker. Also disclosed are a composition and method for noninvasively locating the sentinel lymph node in a mammalian body to determine if cancerous cells have spread thereto.

BACKGROUND OF THE INVENTION

Over 1.1 million breast biopsies are performed each year in the United States alone. Of these, about 80% of the lesions excised during biopsy procedures are found to be benign while about 20% of these lesions are malignant.

Marking and Locating Suspect Tissue Prior to Biopsy

Despite the advances made in technologies such as medical imaging to assist the physician in early stage diagnosis and treatment of patients with possible atypical tissue such as cancer, it is still often necessary to sample difficult-to-reach organ or tissue lesions by biopsy to confirm the presence or absence of abnormalities or disease. In fact, currently, diagnosis requires a tissue sample.

The biopsy is a critical tool used for monitoring breast cancer. The importance of biopsy is more readily understood given that breast cancer is responsible for 18% of all cancer deaths in women and is the leading cause of death among women between the ages of 40 and 55. As with many diseases and other types of cancer, early detection and diagnosis of breast cancer is critical in providing the best chance of survival.

In many cases, detection of the disease is first made when a patient discovers a palpable mass through self-examination and consults her physician. Many times, screening exams, using such diagnostic techniques as x-ray mammography, detects the disease. Other diagnostic techniques also helpful determining the presence of suspect tissue include: digital mammography, scintimammography, ultrasound, magnetic resonance, the Dilon gamma camera, position emission tomography, MIBI imaging, computed topography, fluoroscopy, thermography, transillumination, and diaphanography.

Of these technologies, the primary clinical diagnostic tool for the detection of breast cancer is x-ray mammography. Over 40 million mammograms are performed each year in the United States alone. Mammography uses x-rays to image breast tissue, identifying areas of high density as possible lesions. This technique is used for both screening and diagnostic purposes.

Unfortunately, presently there are significant limitations in technologies, such as mammography, that are able to accurately detect pre-cancerous or cancerous lesions in the breast. Among these limitations is the fact that only approximately one out of every five lesions discovered through x-ray mammography proves to be cancerous. Another limitation is the difficulty in inspecting dense breast tissue that is found in roughly 25% of the population of women. Dense breast tissue is problematic as it is notoriously difficult to inspect via mammography. Also, mammography is generally less effective for women under 40 years of age. For younger women, therefore, self-examination for palpable lesions or ultrasound examination is important. However, neither technique is able to detect microcalcifications, a possible indicator for cancer.

As long as there is a degree of uncertainty associated with these various diagnostic techniques, biopsies must be performed to sample the suspect tissue to determine the tissues exact nature and pathology.

In the detection and treatment of breast cancer, there are two general classes of biopsy: the minimally invasive percutaneous fine or core needle biopsy and the more invasive surgical or "open" biopsy.

Of the less invasive class of percutaneous biopsies, the least invasive is known as a fine needle biopsy. In this case, for palpable lumps, a physician inserts a needle and syringe directly into the lump to obtain a cell sample which is then examined by a cytologist. For non-palpable lesions identified by x-ray mammography or via other diagnostic tools, fine needle biopsies are often performed under stereotactic or ultrasonic guidance. Here, multiple mammograms are taken of the breast and the images are analyzed by a computer to determine the location of the suspect lesion in three dimensions. The physician then penetrates the breast with a needle while targeting the suspect region and removing a small number of cells. There are two significant drawbacks to fine needle biopsy techniques: first, several specimens must be taken to ensure the lesion is well-sampled; second, the limited size of the specimens require the involvement of a skilled cytologist for a proper analysis of the suspect cells in view of the surrounding healthy tissue.

A core biopsy is a second type of percutaneous needle biopsy used to obtain a larger specimen. With this procedure, a larger needle is inserted into the breast via an incision in the skin using stereotactic or ultrasonic guidance. A spring-loaded device is then fired into the breast to obtain a single core sample of tissue, preferably through the center of the lesion. The larger specimen size (up to 20 mm in diameter) obtained by this technique can be more accurately read by a pathologist, who can analyze the suspect cells in the context of the surrounding tissue. Examples of such devices are described in U.S. Patent No. Re. 34,056 and U.S. Patent Nos. 4,944,308 and 4,953,558, the entirety of which are hereby incorporated by reference.

Open biopsies are advisable when suspicious lumps should be removed in their entirety or when core needle biopsies do not render sufficient information about the nature of the lesion.

One such type of open biopsy is the wire localization biopsy. Such a procedure typically is used for non-palpable lesions having a diameter of 7 mm or less as well as for microcalcifications. A wire localization biopsy may also be used to detect small palpable lesions.

This procedure involves several steps described as follows. First, after a local anesthetic is administered, a radiologist inserts a small needle into the breast, typically under x-ray guidance, and moves the needle towards the suspect tissue. The radiologist then passes a wire with a hook on its end through the needle and positions the hook so that the end of the wire is adjacent the suspect tissue. The needle is then removed and a post placement x-ray is taken. The wire is left in the tissue and the patient is then taken to the operating room, sometimes hours later, for the actual open biopsy procedure. Here, the suspect tissue, as marked by the wire, is removed by a surgeon for examination by a pathologist.

Examples of such wire markers are well known in the art; see, e.g., the following patents, the entirety of each which are hereby incorporated by reference: U.S. Patent No. 5,158,084 to Ghiatas, U.S. Patent No. 5,409,004 to Sloan, U.S. Patent No. 5,059,197 to Urie et al., U.S. Patent No. 5,197,482 to Rank, and U.S. Patent No. 5,221,269 to Miller et al.

Despite the advantages of such a technique to locate the suspect tissue for the surgeon, wire localization biopsies have several limitations.

As a first matter, the surgeon sees only the portion of the wire protruding through the skin and has only a general idea of the location of the lesion site. To access the lesion, the surgeon must guide a scalpel along the wire and rely upon the tip of the wire to denote the location of the lesion. Even if the wire has been properly placed by the radiologist, because the surgeon cannot see the tip of the wire (given the surrounding tissue), the surgeon must remove a larger portion of tissue than is necessary to ensure proper excision of the entire mammographic target.

Wire localization techniques have other limitations as well. For one, if the lesion is not found at the end of the wire, the surgeon ends up cutting or removing non-afflicted tissue without removing the lesion. Also, if the tip of the wire penetrates the lesion, the surgeon may sever the lesion by cutting through the tissue along the wire to reach its end. In the latter case, a re-excision may be necessary to remove the entire lesion. Many such procedures require re-excision. Even when a re-excision is performed, the surgeon is still unsure which portion of the original margin is suspect. Due to such problems, surgeons typically make much wider excisions during the original open biopsy procedure and remove more tissue than is necessary to obtain a clean margin.

Another problem occurs when marking lesions in the breast. Two paddles are typically used to compress the breast and stabilize it for placement of the wire. Upon release of the breast from compression, the wire marker can dislodge or migrate to another position away from the suspect tissue. In addition, during the biopsy procedure, the breast is in an uncompressed state as compared to a compressed state during the placement procedure. This change in states renders a different view of the lesion with respect to the healthy tissue. Finally, such wires are often inaccurately placed despite the best efforts of the radiologist. For these reasons, the radiologist must also prepare notations providing instructions to the surgeon on how to find the lesion. These instructions may serve as a backup to confirm the proper location of the needle or to aid the surgeon in finding the suspect tissue in case the needle has migrated.

Various tissue marking systems are known to minimize inadvertent migration of the wire by configuring the wire with a bend or hook. For example, Ghiatas et al., discussed above, has a needle-wire system with a hooked end. U.S. Pat. No. 5,011,473 to Gatturna, the entirety of which is hereby incorporated by reference, teaches a wire having a J-shaped hooked end to immobilize the wire. While the hook configuration may prevent outward wire migration, its shape is not suited to preventing inward migration.

Aside from the above concerns, the mere use of a wire marker possesses inherent problems. After placement, the wire protrudes from the body. Ignoring comfort or cosmetic issues, it is often necessary for the patient to proceed with the surgical removal of the lesion immediately after placement of the wire to minimize the chance of infection, disturbance of the protruding wire, and/or any attendant trauma.

Moreover, the utility of the wire has limitations. Even if a wire does not migrate after placement, a surgeon cannot be sure of the distance from the lesion to the point where the wire protrudes from the skin. Instead, the surgeon can only determine this distance by proceeding along the wire with a scalpel. Furthermore, the surgeon cannot determine the shortest path to access the lesion, rather, the surgeon must always follow the path of the wire, often preventing consideration of a path that may be more cosmetically desirable to the patient, such as a circumareolar approach.

The following references describe other techniques to mark suspect tissue. Each of the following references is hereby incorporated by reference.

A radiopaque marker disclosed in U.S. Patent No. 5,853,366 to Dowlatshahi, addresses some of the physical limitations of the wire as described above.

U.S. Patent No. 5,868,673 to Vesely discloses a system for carrying out biopsy of a tumor by attaching a plurality of reference transducers (piezoelectric crystals) to the surface of an organ, e.g., a breast, and inserting an ultrasonic transducer into a tumor where the internal ultrasonic transducer takes the place of the localization needle.

U.S. Patent No. 6,006,750 to Field discloses a positioning system for marking a specified location within tissue including a hollow needle and localization wire adapted for insertion through the hollow needle into the specified location. A transmitter is connected to the localization wire for transmitting a signal through the tissue so that the specified location within the tissue can be determined when a receiver receives a signal from the transmitter. Field also discloses placement of a stand-alone transmitter adjacent to a lesion.

PCT publication WO 98/30166 discloses a surgical implement detector using a smart marker. The system includes a marker which transmits a predetermined code upon application of a magnetic field in the vicinity, a detecting means reciving the transmitted code and correlates the code with an implement to which the marker is affixed.

PCT publication WO 99/58065 discloses a system and method for bracketing and removing tissue. The system includes a plurality of markers to define the boundary of the tissue volume and a probe and a detector for use in locating the markers by providing information useable by a surgeon that is representative of changes in proximity between the probe and the plurality of markers.

Locating the Site Subsequent to a Biopsy

In cases where a biopsy procedure is performed, a subsequent examination of the biopsy site is very often desirable. There is an important need to determine the location, most notably the center, as well as the orientation and periphery (margins) of the subcutaneous cavity from which the lesion is removed.

For example, in cases where the lesion is found to be benign, a visual, noninvasive follow-up examination of the biopsy site is often performed to ensure the absence of any suspect tissue and the proper healing of the cavity from which the tissue was removed. Such follow-up examination is also performed where the lesion is found to be malignant

and the physician is confident that all suspect tissue was removed and the tissue in the region of the perimeter or margins of the cavity is "clean".

In some cases, however, the physician may be concerned that the initial biopsy failed to remove a sufficient amount of the lesion. Furthermore, in some percutaneous biopsy procedures, such as those using the MAMMOTOME® biopsy probe (JOHNSON & JOHNSON, New Brunswick, NJ), it is very difficult to guarantee clean margins. Such a biopsied lesion is colloquially referred to as a "dirty lesion" or "having a dirty margin" and requires follow-up observation of any suspect tissue growth in the surrounding marginal area of the initial biopsy site. Thus, an excision around the original biopsy site must often be performed. In such a case, the perimeter of the cavity should preferably be identified, as the cavity may contain cancerous cells. Identification of the cavity perimeter is desirable to avoid the risk of opening the cavity, which could release and spread the cancerous cells. Marking the biopsy site is further useful for indicating where a needle should be inserted for injection of radiotherapeutic or chemotherapeutic agents that may be used to debulk a tumor prior to re-excision, for injection of migratory agents for indicating sentinel nodes, or for injection of lidocaine or other local anesthetic prior to re-excision. Moreover, the site of the re-excised procedure itself requires follow-up examination, providing further impetus for accurate identification of the location of the re-excised site. Therefore, a new marker may be placed after re-excision for further biopsy or lumpectomy. In addition to aiding in follow-up examination, marking a lumpectomy site is further useful for indicating where a needle should be inserted for injection of radiotherapeutic, chemotherapeutic, or other agents that may be used for local therapy.

Prior methods of marking biopsy cavities utilize one or more tissue marking clips as the biopsy site-marking device. Most commonly, these marker clips have a "horseshoe" configuration. The marker clips attach to the walls of the cavity when the free ends or limbs of the "horseshoe" are pinched together, trapping the tissue. This device has significant drawbacks.

For instance, prior to placing the marker clip at the cavity site, care must be taken to remove residual tissue debris, typically by vacuum, to minimize the possibility that the marker clip attaches to any loose tissue as opposed to the cavity wall. Once the cavity is prepared, the clip must be examined to ensure that the limbs of the clip are substantially straight. If the limbs have been prematurely bent together, the clip will be discarded, as it

will most likely not attach properly to the cavity wall. Actual placement of the clip often requires additional vacuum of the cavity wall to draw the wall into the aperture between the limbs of the marking clip so that a better grip is obtained between the limbs of the clip. Additionally, there is always the possibility that the clip may detach from the cavity wall during or after withdrawal of the tools used to place the clip into the cavity.

Aside from the problems inherent in the placement of the marking clip, there are also limitations associated with how well the marking clip can identify a biopsy cavity. As the marking clip must trap tissue for proper attachment, in cases of endoscopic, fluoroscopic, or blind placement, the clip can only be placed on a wall of the cavity substantially opposite to the opening of the cavity.

Moreover, patient concern may limit the number of clips that may be placed in a cavity. As a result, the medical practitioner is forced to identify the outline of a three dimensional cavity by a single point as defined by the marking clip. Obviously, determination of the periphery of a biopsy cavity from one point on the periphery is not possible.

These limitations are compounded as the biopsy cavity fills within a few hours with bodily fluids, which eventually renders the cavity invisible to noninvasive techniques. Another difficulty in viewing the clip stems from the fact that the clip is attached to the side, not the center, of the cavity. This makes determining the spatial orientation and position of the cavity difficult if not impossible during follow-up examination. Additionally, during a stereotactic breast biopsy procedure, the breast is under compression when the marking clip is placed. Upon release of the compressive force, determining the location of the clip can be unpredictable, and any information once known about the orientation and location of the periphery of the cavity is lost.

The marker clip does not aid in the healing process of the biopsy wound. Complications and false information may arise if the marker strays from its original placement site. As described above, if a re-excision of the site is required, the marker clip may also interfere when excision of a target lesion is sought.

Other devices pertaining to biopsy aids are directed to assisting in the healing and closure of the biopsy wound, but they do not address the clinical need or desire of accurately preserving the location and orientation of the biopsy cavity. See, e.g., U.S.

Patent Nos. 4,347,234; 5,388,588; 5,326,350; 5,394,886; 5,467,780; 5,571,181; and 5,676,146.

Location of Sentinel Nodes

In cases where a biopsy excises a lesion or tumor suspected to be cancerous, it is desirable to determine whether any cancerous cells have spread from the site of the original lesion or tumor. A sentinel node (SN) is the first lymph node, or one of the first lymph nodes, to receive drainage of lymphatic fluid and cells from a tumor or malignant growth. For various cancers such as malignant melanoma and breast cancer, identification of the SN is now a standard technique for determining whether cancerous cells have migrated to a lymph gland from the site of the original lesion or tumor. Increasing data suggest that the status of the SN may predict whether other nodes in the axilla (i.e. the armpit) harbor cancerous cells. Although identification of the SN may be desirable after some biopsy procedures, there are occasions where identification of the SN is desirable even though no biopsy procedure is performed. In fact, a thorough analysis of multiple sections (0.5-mm intervals) of a sentinel node or nodes is more likely to detect hidden micrometastases than a routine single-section examination of many regional nodes, including the sentinel node, according to Jannink et al. in "Serial Sectioning of Sentinel Nodes in Patients with Breast Cancer: A Pilot Study," *Annals of Surgical Oncology*, 5(4):310-314.

Thus, accurately determining the location of a SN permits removal of the SN to determine its pathology. If the SN does not contain cancerous cells, the cancer has not spread and the stage of the cancer can be determined. The ability to make this determination from an examination of the SN minimizes the number of lymph nodes removed and eliminates the need to remove additional lymph nodes. In a review in Breast Diseases: A Year Book® Quarterly Vol. 10 No. 3, of a paper by Hack et al., "Physical and Psychological Morbidity After Axillary Lymph Node Dissection for Breast Cancer," J Clin Oncol 17:143-149, 1999, Vetto states that approximately 27% of patients undergoing sentinel lymph node biopsy for early-stage breast cancer still require axillary lymph node dissection (ALND) due to the existence of a positive node. Accordingly, the remaining 63% of the patients would benefit from a SN biopsy by avoiding radical dissection.

Previously, it was impossible to locate the sentinel node without performing ALND. In the case of breast cancer, determining whether the cancerous cells migrated involved

removal of all axillary lymph nodes. This required radical surgery. This painful option often lead to complications that resulted in significant morbidity and even mortality. As discussed by Hack et al., pain and discomfort after ALND significantly corresponded to quality of life after the procedure. According to Hack et al., patients with more than 13 lymph nodes dissected reported more pain than women with fewer lymph nodes dissected.

More recently, a technique known as "sentinel node biopsy" allows for accurate mapping of a SN's location by the use of blue dye and a radioactive tracer, separately or in combination. Typically, a dye and/or a radioactive tracer are injected around the location of a tumor into the biopsy cavity or tumor cavity (if the tumor was partially or completely removed), or "subdermally" into the parenchymal tissue anterior to the tumor. This latter technique is described by De Cicco et al. (1999) in "Lymphoscintigraphy and Radioguided Biopsy of the Sentinel Axillary Node in Breast Cancer," *J Nucl Med* 39:2080-2084, 1998, and in a review of that article by Haigh et al. in Breast Diseases: A Year Book® Quarterly, Vol. 10, No. 3 (1999). The dye migrates from the tumor site through the lymphatic channels to the regional lymph nodes that serve the cancerous tissue. The SN, which is the node most likely to be involved with cancer, is identified through surgery and removed for pathologic analysis. When a radioactive tracer is used, a gamma probe or like-device is used to further assist a physician in identifying the site of the SN.

Unfortunately, visualization of the blue dye depends upon the surgeon localizing it, and no preoperative assessment of mapping is possible. Therefore, the surgeon must first make an incision in the general vicinity of the lymph nodes, then dissect around the area to locate the blue dye. Another complication arises as the dye may cause an allergic reaction in some individuals. The blue dye may leave a mark on the skin similar to a 'tattoo.'

Using a radioactive tracer, alone or in combination with blue dye, to locate the SN also has some disadvantages. It is an interdisciplinary process, requiring nuclear medicine personnel, adherence to radiation safety regulations, preparation of the radiocolloid, and gamma detection instrumentation. Furthermore, the safety of this procedure is questionable. See e.g., Miner et al., "Guidelines for the Safe Use of Radioactive Materials During Localization and Resection of the Sentinel Lymph Node," *Ann Surg Oncol* 6:75-82 (1999).

In the case of a lumpectomy, when the lesion is known to be cancerous, locating the SN is desirable so that the SN is removed in the same procedure as the lumpectomy. In

fact, even if the pathology of the lesion is not yet known, there are reasons for initiating the SN localization during a breast biopsy procedure, as discussed below.

Previously, imaging techniques, such as ultrasound, MRI, and CT, attempted to non-invasively find and diagnose cancerous lymph nodes prior to removing them. However, according to Schlag, "The 'Sentinel Node' Concept: More Questions Raised than Answers Provided?" *Oncologist* 3(5):VI-VII (1998), general criteria such as size, shape, structure, or texture in the various imaging modalities are unreliable, and these techniques result in low sensitivity and/or low specificity. As described by Veronesi et al., "Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes," *Lancet* Jun 28; 349(9069):1864-7 (1997), in 32 (38%) of 85 patients with metastatic axillary nodes, the only positive node was the sentinel node. Accordingly, if all of the nodes were checked by imaging instead of locating and biopsying the SN, the chances of missing the cancer would likely have been much higher. Furthermore, because of usually low specificity, these techniques require surgical excision and examination of multiple lymph nodes, many of which may contain no cancer. In contrast, by identifying only one or a few SN's, without trying to make any diagnosis of cancer prior to tissue removal, the excision is much less extensive, yielding a smaller tissue sample. Also, the histological examination of one or a few SN's can be more thorough than the case where many lymph nodes require examination.

Based upon the above, a need remains for a surgeon to be able to accurately determine both the location of a previously marked lesion and the distance to that lesion from a given point outside the body. Such a system should eliminate the need for a wire marker, allow a surgeon to instantaneously select the shortest or most cosmetically desirable path to the suspect tissue as the tissue is being manipulated, and permit any margin to be ascertained with higher accuracy so that only targeted tissue is removed, if any.

Another objective of the invention described herein is to provide a marking device, delivery device, and method that enable noninvasive determination of cavity location, orientation, and periphery.

Another objective is to provide an atraumatic marking device that does not rely on pinching or piercing tissue to mark a cavity.

Another objective is to provide a method of delivering through a small opening a marking device for marking the borders of a cavity.

Another objective is to provide a composition and method for localizing and marking a sentinel node.

Another objective is to provide a composition capable of (1) deposition in or around a lesion and migration to and accumulation in the associated sentinel node, and (2) noninvasive detection.

Another objective is to provide a method for remotely detecting the location of a sentinel node with a minimum of trauma and toxicity to the patient.

Yet another objective is to provide a composition and method for both marking a lesion cavity and locating the sentinel node in the same procedure.

SUMMARY OF THE INVENTION

This invention relates to devices and procedures for determining the location and the distance of a detectable smart marker relative to a surgical instrument having sensors which are able to detect the smart marker. In particular, the invention comprises a smart marker for marking a location within tissue, a device for modifying the tissue, and at least one sensor disposed on the device for sensing proximity and direction to the smart marker.

A feedback device for relaying proximity sensor information to the user is also included. This device may be a visual display (graphic or alphanumeric or both), a virtual reality display, a tactile display, an audio feedback device, and/or a combination thereof.

The tissue can be modified by cutting, radiation, chemical means, ablation, or coagulation. The system can utilize mechanical energy, cryoablation energy, radio frequency energy, microwave energy, ultrasonic energy, chemical energy, electrochemical energy, thermal energy, optical energy (e.g., laser energy), or any combination thereof to modify the tissue.

Tissue can be either removed by the inventive device or contain a separate tissue removal device.

The marker can be magnetic, radiopaque, bioabsorbable, or any combination thereof. Examples of the sensor include magnetic, preferably ultrasonic, magnetoresistive, inductive, a Hall effect, pulse doppler, radioactive, Geiger-Müller counter, thermal,

infrared, or light sensor. Obviously, the marker and the sensor will be selected so that they are compatible with each other.

The invention also is a system for tissue modification comprising a fixed reference point, a first proximity sensor for marking the tissue to obtain first proximity information of the tissue with respect to the first reference point, a device for modifying the tissue, a second proximity sensor disposed on the device for obtaining second proximity information of the device with respect to the fixed reference point, and a device for, perhaps, determining a distance between the first and the second proximity sensors using the first and the second proximity information. The fixed reference point can comprise at least one marker (e.g., a magnet.)

Another aspect of the invention comprises a remotely detectable smart marker, a surgical cutting device comprising at least one sensor to detect the smart marker, the sensor in communication with a computer, and a computer readable medium configured to translate a signal from the sensor to a feedback device.

Another aspect of the invention comprises at least one sensor capable of detecting a smart marker disposed in tissue, the sensor in communication with a control system adapted to instantaneously determine a location of the smart marker in space and a distance of the smart marker relative to the sensor as tissue is modified.

The invention also includes a computer-readable medium containing instructions for controlling a computer system to display (1) information regarding a location of a detectable smart marker disposed within tissue and (2) information regarding a distance of the smart marker relative to at least one sensor by analyzing at least one signal generated by the sensor containing the location information and the distance information, converting the signal into a computer readable data, and transforming the computer readable data into data readable by a feedback device and easily interpreted by a clinician.

Yet another aspect of the invention includes a method for modifying tissue in a patient comprising the steps of inserting into the patient a tissue-modifying device having a proximity sensor adapted to detect a previously placed smart marker, directing the device to the tissue to be modified using the proximity sensor, and modifying the tissue.

At least a portion of the tissue can be removed from or left in the patient. The patient may leave a facility at which the method takes place after the smart marker has been

deployed in the tissue but before inserting the tissue-modifying device into the tissue. The smart marker can either be removed from or left in the patient.

The invention also includes a method for determining a location and a distance of a lesion in a mass of tissue relative to a surgical cutting device comprising the steps of detecting the lesion marked by a detectable smart marker with the surgical cutting instrument, approaching the lesion with the surgical cutting instrument, and removing the lesion from the mass of tissue.

The invention also includes a method for determining a location and distance of a lesion in a mass of tissue relative to a surgical cutting device comprising the steps of deploying a detectable smart marker within the mass of tissue to mark a volumetric center of the lesion, detecting the detectable smart marker with the surgical cutting instrument, approaching the lesion with the surgical cutting instrument, and removing the lesion from the mass of tissue.

This invention also relates to devices and procedures for percutaneously marking a biopsy or lumpectomy cavity, or a cavity created by removal of one or more sentinel nodes. In particular, the inventive device is a biopsy cavity marking body made of a resilient, preferably bioabsorbable material having at least one radiopaque, echogenic, or otherwise detectable marker. Also, the marker could be an active device that responds to external excitation (e.g., a semiconductor micro-machine). The device may take on a variety of shapes and sizes tailored for the specific biopsy cavity to be filled. For example, the device in its simplest form is a spherical or cylindrical collagen sponge having a single radiopaque or echogenic marker located in its geometric center. Alternatively, the body may have one or more components linked together with multiple radiopaque or echogenic markers. One variation of the invention includes a marker that is affixed about an outside surface of the filler body. The size of the marker may be determined as needed for the particular application. The detectable marker may also be deposited on the filler body by a method such as, including but not limited to, painting, coating, dipping, spraying, and/or co-extruding.

A further aspect of the invention allows the marker or the body, singly or in combination, to be constructed to have a varying rate of degradation or bioabsorption. For instance, the body may be constructed to have a layer of bioabsorbable material as an outer "shell." Accordingly, prior to degradation of the shell, the body is palpable. Upon

degradation of the shell, the remainder of the body would degrade at an accelerated rate in comparison to the outer shell. However, other variations of the invention need not rely on palpability and may or may not be palpable. For example, in a variation of the marking device having a shell, the body of the device may contain air which increases the echogenic properties of the marking device. Accordingly, the device may be detectable, for example, by ultrasonic detection.

The invention also includes a marking device comprising a filler body comprising a bioabsorbable material and a detectable shell covering the body. The shell may be porous, or comprised of a silicone rubber in which case the shell is designed so that the bioabsorbable filler body is absorbed into the body. In one variation the bioabsorbable material may comprise a bioabsorbable liquid. The invention may include an adhesive located on an outer surface of the shell. Another variation includes the body comprising collagen with the shell comprising an adhesive.

The marking device may additionally contain a variety of drugs, such as hemostatic agents, photo-therapeutic agents, pain-killing substances, or even healing or therapeutic agents that may be delivered directly to the biopsy cavity. Furthermore, the material and configuration of the sponge itself may be hemostatic. Importantly, the device is capable of accurately marking a specific location, such as the center, of the biopsy cavity, and providing other information about the patient or the particular biopsy or device deployed.

The marking device is preferably, although not necessarily, delivered immediately after removal of the tissue specimen using the same medical instrument used to remove the tissue specimen itself. Such medical instruments are described in U.S. Patent Nos. 5,111,828; 5,197,484; 5,353,804; 5,511,566; 5,546,957; 5,560,373; 5,817,033; 6,036,698; and pending U.S. Patent Application Serial No. 09/145,487, filed September 1, 1998 and entitled "PERCUTANEOUS TISSUE REMOVAL DEVICE." The marking device is compressed and loaded into the delivery device and percutaneously advanced to the biopsy site where, upon exiting from the delivery device, it expands to provide friction to keep the device within the cavity, or, to substantially fill the cavity from the biopsy. The physician may then use follow-up noninvasive detection techniques, such as x-ray mammography or ultrasound, to identify, locate, and monitor the biopsy cavity site over a period of time.

The marking device is usually inserted into the patient's body either surgically via an opening into the body cavity, or using a minimally invasive procedure employing such

medical instruments as a catheter, introducer, biopsy probe, or similar device, or a specially-designed delivery device used alone or in conjunction with a catheter, introducer, biopsy probe, or similar device. When inserted via the minimally invasive procedure, the resiliency of the body allows the marking device to be compressed upon placement in a delivery device. Upon insertion of the cavity marking device into the cavity, the resiliency of the body causes the cavity marking device to self-expand, substantially filling the cavity. Following expansion, the marking device volume following expansion preferably is 3 to 30 times its compressed volume, and more preferably 5 to 22 times, and most preferably about 10 times. The resiliency of the body can be further predetermined so that the body is palpable, thus allowing tactile location by a surgeon in subsequent follow-up examinations. When used in this way, typically, the filler body is required to be palpable for approximately 3 months. However, this period may be increased or decreased as needed.

The expansion of the resilient body can be aided by the addition of a biocompatible fluid, which is absorbed into the body. For instance, the fluid can be a saline solution, a painkilling substance, a healing agent, a therapeutic fluid, or any combination of such fluids. The fluid or combination of fluids may be added to and absorbed by the body of the device before or after deployment of the device into a cavity. For example, the body of the marking device may be presoaked with the fluid and then delivered into the cavity. In this instance, the fluid aids the expansion of the body of the device upon deployment. Another example is provided as the device is delivered into the cavity without being presoaked. In such a case, fluid is delivered into the cavity after the body of the device is deployed into the cavity. Upon delivery of the fluid, the body of the device soaks up the fluid, thereby aiding the expansion of the cavity marking device as it expands to fit the cavity. The fluid may be, but is not limited to being, delivered by the access device. Furthermore, expansion of the body of the marking device may be aided by body fluids, such as the fluid component of blood, already present in the cavity.

By "biocompatible fluid" what is meant is a liquid, solution, or suspension that may contain inorganic or organic material. For instance, the biocompatible fluid is preferably saline solution, but may be water or contain adjuvants such as medications to prevent infection, reduce pain, or the like. Alternatively or additionally, the fluid may be used to mark the sentinel lymph node, as will be described later. Obviously, the liquid is intended to be a type that does no harm to the body.

After placement of the cavity marking device into the cavity, the bioabsorbable body degrades at a predetermined rate. As the body of the cavity marking device is absorbed, tissue is substituted for the bioabsorbable material. Moreover, while the body degrades, the marker, which is usually suspended substantially in the volumetric center of the body of the device, is left in the center of the cavity. Thus, during a subsequent examination, a medical practitioner having knowledge of the dimensions of the body of the cavity marking device can determine the location as well as the periphery of the biopsy cavity. The orientation of the cavity is self-evident as the marker is left in substantially the center of the cavity. For the case where multiple markers are used, the markers are usually placed in a manner showing directionality.

The body, marker, or radiopaque or echogenic coatings can be made to degrade *in situ* and be absorbed into the patient's body over a predetermined period of time. It is generally preferred that if the marker's radiopacity or echogenicity is chosen to degrade over time, such degradation does not take place within at least one year after implantation of the inventive device. In this way, if a new lump or calcification (in the case of a breast biopsy) is discovered after the biopsy, such a marker will allow the physician to know the relation of such new growth in relation to the region of excised tissue. On the other hand, and as discussed below, a bioabsorption period of three months is preferred for any such coatings on the perimeter of the body itself.

Another variation of the invention is that the body of the marking device is formed from a bioabsorbable thread-like surgical material, for example a suture material. Preferably, the surgical material is resilient. In this variation the surgical material is looped through a marker. The marking device may have any number of loops or any number of opposing pairs of loops. Another variation of the marking device includes an opposing member on each loop. For example, a loop could be folded to form the opposing member. Another variation of the invention includes using a thread-like material inside of a filler body where the thread-like material functions as the marker. In such a case, the thread-like material may be spirally wound within the filler body.

The invention further includes a method and device for marking a cavity using a bioabsorbable material in a thread-like form and filling the cavity with the bioabsorbable material until the material occupies a substantial volume of the cavity. The device

mentioned above may include a delivery means for delivering the bioabsorbable material to the cavity in a thread-like configuration.

This invention further includes the act of filling the biopsy cavity with a bioabsorbable liquid, aerosol or gelatinous material, preferably gelatinous collagen, allowing the material to partially solidify or gel and then placing a marker, which may have a configuration as described above, into the center of the bioabsorbable material. The gel may also be made radiopaque or echogenic by the addition of radiopaque or echogenic materials, such as powdered tantalum, tungsten, barium carbonate, bismuth oxide, barium sulfate or other barium- or bismuth-containing compounds.

This method may be combined with any aspect of the previously described devices as needed. For instance, one could insert a hemostatic or pain-killing substance as described above into the biopsy cavity along with the bioabsorbable material. Alternatively, a bioabsorbable marker could be inserted into a predetermined location, such as the center, of the body of bioabsorbable material.

It is within the scope of this invention that either or both of the marker or markers and the bioabsorbable body may be radioactive, especially if a regimen of treatment using radioactivity is contemplated. Alternatively or additionally, the body of the cavity marking device may temporarily accommodate a radiopharmaceutical.

This procedure may be used in any internal, preferably soft, tissue, but is most useful in breast tissue, lung tissue, prostate tissue, or lymph gland tissue. Obviously, though, treatment and diagnosis of breast tissue problems forms the central theme of the invention.

In contrast to the marker clips as described above, the cavity marking device has the obvious advantage of marking the geometric center of a biopsy cavity. Also, unlike the marking clip which has the potential of attaching to loose tissue and moving after initial placement, the marking device self-expands upon insertion into the cavity, thus providing resistance against the walls of the cavity thereby anchoring itself within the cavity. The marking device may be configured to be substantially smaller, larger, or equal to the size of the cavity; however, in some cases the marking device will be configured to be larger than the cavity. This aspect of the biopsy site-marking device provides a cosmetic benefit to the patient, especially when the biopsy is taken from the breast. For example, the resistance provided by the cavity marking device against the walls of the cavity may minimize any

"dimpling" effect observed in the skin when large pieces of tissue are removed, as, for example, during excisional biopsies. The marking device may be configured to allow tissue ingrowth, being replaced by tissue as it is absorbed into the patient's body.

The invention further includes a delivery device and method for placement of a marking device. For example, the invention includes a sheath capable of being placed in contact with a cavity, a cartridge or applicator in which a marking device may be placed, and a disengaging arm onto which the cartridge is mounted. The marking device will preferably have a frictional fit with the cartridge. Preferably, the sheath is placed in contact with the cavity, for example, simultaneously with the biopsy device or soon after the biopsy device obtains a sample. The sheath may be placed at a point of entrance of the cavity or it may be partially inserted into the cavity. The delivery device cartridge and engaging arm are then inserted into the sheath and advanced into the cavity until a portion of the cartridge containing the marking device is positioned within the cavity but a portion of the cartridge is still within the sheath. Next, the delivery device cartridge is retracted while the disengaging arm prevents the marking device from being retracted from the cavity. Thus, the marking device remains in the cavity and radially expands to substantially fill the cavity. Hence, the marking device is delivered and expands in the cavity without a need for simultaneously pushing the marking device into the cavity. Another aspect of this invention is that the frictional fit between a marking device and a cartridge may be sufficiently increased to minimize premature placement of the marking device into the cavity.

Other delivery devices and methods for using them are disclosed, including a "sheath-over-probe" device and method and "through-cannula" devices and methods. These devices and methods are well suited to apply the marking device having a body comprising absorbable suture or collagen and described herein, but could be used with any of the marking devices in the present application.

The "sheath-over-probe" device includes a sheath that slides over a probe, such as a biopsy probe. It is well suited for use with the MAMMOTOME® 11 GA Probe but may be sized to fit other commercially available biopsy devices. The sheath is introduced into the body along with the probe. After obtaining a biopsy sample, the probe is removed, leaving the sheath in place. The marking device is then delivered through the sheath.

The "through-cannula" device is intended for insertion through the cannula portion of a biopsy device; it, too, is well suited for the MAMMOTOME® 11 GA Probe but may be sized to fit other commercially available biopsy devices.

Although the subcutaneous cavity marking device and methods described above are suited for percutaneous placement of the marker within a biopsy cavity it is not intended that the invention is limited to such placement. The device and method are also appropriate for intraoperative or surgical placement of the marker within a biopsy cavity.

The present invention also provides an alternative method to remotely detect sentinel nodes (SN). This method includes the deposit, preferably by injection via a thin needle applicator or using a marker delivery device described herein, of a remotely detectable contrast agent that will migrate to the SN, allowing the exact location of the SN to be pinpointed and targeted for removal using minimally invasive techniques. This method eliminates the need for potentially toxic radioactive tracer material. In addition, the lack of toxicity of such agents obviates the need to remove the lesion and/or the SN on the same day.

These agents may be any biologically compatible agents capable of remote detection. Examples of such remote detection include, but are not limited to magnetism such as a magnetometer, Hall effect sensor, or magnetic resonance imaging (MRI); ultrasound; thermal means; high intensity ultraviolet techniques; fluorescent dye techniques; singly or in combination.

One example of such a contrast agent is an echogenic microsphere capable of reflecting ultrasonic energy. These microspheres, which average typically between 0.2 microns and 5 microns in diameter, may be mixed with a biologically compatible carrier-fluid and injected into the body in the vicinity of the lesion. Upon an exposure to ultrasonic energy, the spheres reflect the energy creating an ultrasonic reflection. The ultrasonic reflection resulting from a large number of the microspheres that have accumulated in the SN permits detection of the particular node by a conventional ultrasonic probe. Such microspheres are available at various pharmaceutical companies such as Acusphere, Sonus, and Alliance Pharmaceutical Corp.

Another example of a detectable agent is a biologically compatible magnetically detectable body such as a magnetic microsphere. Such a magnetically detectable body can be the echogenic microsphere described above that is either fabricated from or coated with

a magnetic material. Alternatively, the magnetically detectable body may be a solid or other type of magnetic body capable of being incorporated into a carrier fluid and deposited around the lesion or its cavity as described above. These bodies are preferably capable of migration to and accumulation in the SN so that, in a similar fashion to the echogenic microspheres, the cumulative magnetic field produced by these magnetic bodies allows for location of the SN by remote and noninvasive means.

Yet another such contrast agent is a radiopaque fluid or suspension containing radiopaque particles, detectable using X ray, fluoroscopy, or computed tomography (CT). Again, this contrast agent is preferably capable of migration to and accumulation in the SN to enable one to noninvasively determine the location of the SN.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1Q illustrate various configurations of the device of the present invention.

Figure 1A illustrates a tissue cavity marking device with a spherical body and a single centrally located marker.

Figure 1B shows a tissue cavity marking device with a cylindrical body and two ring-shaped markers aligned near the cylinder's longitudinal axis.

Figure 1C shows another tissue cavity marking device with a multifaced or irregular body and a single centrally located marker.

Figure 1D illustrates a tissue cavity marking device with a body having pores.

Figure 1E is a partial cross-sectional view of Figure 1D.

Figure 1F illustrates a tissue cavity marking device with a body having an outer shell of a bioabsorbable material.

Figures 1G-1J illustrate various configurations of the device having a body comprising suture-type material.

Figure 1G illustrates a tissue cavity marking device with a number of loops.

Figure 1H illustrates a tissue cavity marking device with a pair of opposing loops.

Figure 1I illustrates a tissue cavity marking device with two pairs of opposing loops.

Figure 1J illustrates a tissue cavity marking device having a pair of opposing loops where the loops are longitudinally folded forming opposing members.

Figure 1K illustrates a tissue cavity marking device with two pairs of opposing loops where each loop is longitudinally folded forming opposing members.

Figures 1L and 1M illustrate tissue cavity marking devices having an elongated body having circular or rectangular cross section and a metallic marker band oriented with its axis perpendicular to the long axis of the body.

Figures 1N and 1O illustrate tissue cavity marking devices having a marker that is crimped or press fit about an elongated body.

Figure 1P illustrates a tissue cavity marking device having markers that are deposited on a thread-like body.

Figure 1Q illustrates a tissue cavity marking device having a marker where the marker is a shell covering the body and the shell marks the perimeter of the cavity.

Figures 2A-2H illustrate various configurations of the marker of the device.

Figure 3A illustrates a cavity marking device having multiple body components traversed by a single wire or suture marker, or multiple wires or suture markers.

Figure 3B illustrates a cavity marking device having a helically wound wire or suture marker.

Figure 3C illustrates a cavity marking device having wire or suture markers on the perimeter of the body.

Figure 3D illustrates a cavity marking device having wire or markers on the ends of the body.

Figures 3E-3G illustrate cavity marking devices having a spirally or helically coiled marker within or wrapped about a body.

Figures 3H -3J illustrate cavity marking devices having a coiled marker within or wrapped about a body and partially extending from one end of the body.

Figure 3K illustrates a cavity marking device comprising three bioresorbable layers having various resorption rates.

Figures 4A-4C illustrate a method of marking a biopsy tissue cavity with the device of the present invention.

Figures 4D-4F illustrate a method of marking a biopsy tissue cavity with the device of the present invention wherein a biocompatible fluid is delivered to the cavity marking device after placement.

Figures 4G-4I illustrate a method of marking a biopsy tissue cavity with the device of the present invention wherein a biocompatible fluid is used to push the cavity marking device out of the access device and into the biopsy tissue cavity.

Figures 4J-4L illustrate a method of marking a biopsy tissue cavity with the device of the present invention wherein the body material of the marking device is deposited into the biopsy cavity prior to the placement of the marker within the biopsy device.

Figures 4M-4N illustrate insertion of a detectable material into a cavity where the detectable material has a thread-like form.

Figure 4O-4P illustrates a method of marking a biopsy tissue cavity with a device of the present invention where the marker has a shell and a degradable body.

Figures 5A-5B illustrate a spherical wire marking device for deployment without a filler body into a tissue cavity.

Figure 5C illustrates a cylindrical wire marking device for deployment without a filler body into a tissue cavity.

Figures 5D-5E illustrate a helical coil wire marking device for deployment without a filler body into a tissue cavity.

Figures 6A-6D illustrate a method for marking a biopsy tissue cavity with the marking device of the present invention wherein the marking device expands into the cavity without the need for simultaneous pushing of the marking device into the cavity.

Figures 7A-7K illustrate devices for marking a biopsy tissue cavity with the marking device of the present invention.

Figures 8A-8I illustrate a variation of a delivery device and a method for using it to deliver a marking device to a tissue cavity made by the probe of a medical instrument.

Figures 9A-9F illustrate a variation of a delivery device and a method for using it to deliver a marking device to a tissue cavity through the cannula of a medical instrument.

Figures 10A-10H illustrate another variation of a delivery device and method for using it to deliver a marking device to a tissue cavity through the cannula of a medical instrument.

Figures 11A-11E illustrate another variation of a delivery device and method for using it to deliver a marking device to a tissue cavity through the cannula of a medical instrument.

Figures 12A-12C illustrate a method for locating a sentinel node.

Figures 13A-13B illustrate a method for marking a biopsy or lumpectomy cavity and locating a sentinel node.

Figure 14 shows an exemplary detectable smart marker encapsulated in a sphere and ready for insertion through an insertion device.

Figure 15 shows the tissue modification system of the present invention in the form of a Bovie device equipped with a sensor, RF generator, interface, computer, and feedback device.

Figure 16 is a schematic depicting the basic functions performed by the software of the invention to transform positional data into data useable by a feedback device.

Figure 17 is an exemplary screen and control panel for a feedback device.

Figure 18 is another exemplary feedback device in the form of a simple flat screen displaying three-dimensional position data.

Figure 19 depicts a method of practicing the invention comprising circumareolar access of an implanted smart marker in breast tissue to remove suspect tissue using a Bovie equipped with the remote sensing device.

Figure 20 illustrates a shell, or envelope, created around a virtual marker for use with the invention.

DETAILED DESCRIPTION OF THE INVENTION

The following illustrations are examples of the invention described herein. It is contemplated that combinations of aspects of specific embodiments or combinations of the specific embodiments themselves are within the scope of this disclosure.

This invention includes a tissue modification apparatus and method for accurately marking and locating a lesion or other suspect tissue. Often, the inventive tissue modification device will be a surgical cutter adapted with at least one proximity sensor for detecting the location and distance of a remotely detectable smart marker. A method for using the inventive tissue modification device is also disclosed.

This invention also variously comprises a remotely detectable smart marker, a control system, a computer-readable medium, and feedback apparatus such as a visual display, audible feedback and/or tactile feedback. In operation, once the remotely detectable marker is deployed in the tissue of interest, the tissue modification device is used to modify tissue, perhaps by removing the tissue. This removal is accomplished while

determining and comparing the instantaneous location of the smart marker in space and the instantaneous distance of the marker relative to a sensor associated with the cutting device to guide that cutting device to the marker. The set up of the operating room may appear much like that used for laparoscopic or endoscopic surgery in that a physician may manipulate a tool in a patient while watching a video monitor for guidance. Preferably, the targeting system will be intuitive to a surgeon familiar with such procedures. As an alternative, the physician may watch a read out of distance to the smart marker on the tissue modification device itself.

What follows is a description of the apparatus and method of the invention, organized by the various components of the apparatus and its method of use.

Smart Marker

Figure 14 shows a typical marker 2100 for use in the present invention. This marker may be termed a "smart marker" in the sense that it is capable of being remotely detected by the apparatus described herein. The marker of Figure 14 is merely exemplary; the marker of the present invention is not so limited as it may be combined with various other features of markers described herein.

Smart marker 2100 should be made of any remotely detectable material that is preferably radiopaque and more preferably magnetic, but may also be ultrasonically echogenic or an externally excited active marker capable of responding to external stimuli. By the terms "magnetic" and the like, we mean any body or material that possesses some level of ferromagnetism or paramagnetism, and particularly a level which is detectable by the proximity sensor described below.

While one use of the smart marker is to mark, for removal, a lesion with a confirmed diagnosis of cancer, the smart marker may alternatively be deployed into a biopsy cavity at the time of or following tissue sample removal but prior to diagnosis. Therefore, the smart marker should be one which is safe for placement into the region of suspect tissue or a cavity and remain there, if necessary, indefinitely. For instance, it is contemplated that although the smart marker 2100 may be immediately removed within hours or even minutes of its placement, it may, on the other hand, remain deployed in the tissue for days, months, or years; even indefinitely. Alternatively, the smart marker 2100 may be bioabsorbable.

Optimally, as shown in Figure 14, the remotely detectable or magnetically detectable smart marker 2100 may have a spherical shape with a preferable diameter D of approximately 2.0 mm, although diameter D (or the widest dimension if not spherical or round) may be as large as 20 mm or more or as small as 0.1 mm or less. The particular dimensions of the smart marker will be dictated by the application in the tissue of interest (i.e., breast, liver, lungs, etc.), the size of the suspect lesion, tissue, or tissue cavity, the apparatus used to deploy the smart marker, the condition of the patient, the timeframe during which the smart marker is expected to remain in the tissue, the shape of the smart marker, the type of surgical device used to access the smart marker, the sensitivity of that device to be able to remotely detect the location of the smart marker in space, and the distance of the smart marker from the surgical device containing the sensors, etc.

Figure 14 shows smart marker 2100 as comprising an internal detectable component 2120, such as a disk or sphere, encapsulated in a biocompatible covering or container 2140. The detectable component 2120 can comprise stainless steel (to the extent that a particular stainless steel is ferromagnetic and is detectable), various rare earth materials, ferromagnetic materials, magnetic composite materials, and alloys of these. Examples of biocompatible coverings or containers 2140 include biologically inert metals and their alloys (such as platinum, gold, titanium, etc.), collagenous or fibrous material, and various thermoplastic materials as are well-known in the medical arts. The smart marker 2100, detectable component 2120, and covering 2140 can also be bioabsorbable, such that over a predetermined time it is absorbed into the surrounding tissue as dictated by the particular application for which the smart marker is used.

Although the smart marker 2100 is shown as comprising component 2120 and covering 2140, it may comprise either of these devices alone or in conjunction with other components (such as various bioactive drugs or therapeutic materials), as long as it is remotely detectable as described herein. A variation of the smart marker may also include a smart marker that is made of a bioabsorbable material with a known/selected decomposition rate, eliminating the need for later removal and thus eliminating the possibility of an additional invasive procedure.

The smart marker may take on a variety of shapes. For instance, the smart marker 2100 may be spherical (either solid or hollow) as shown in Figure 14, or it may be asymmetric so that one may determine its spatial orientation after deployment in a patient's

tissue or cavity (via magnetic resonance imaging (MRI), fluoroscopy, or other techniques). The smart marker may be shaped such that, after placement, it encounters equal pressure from all sides (e.g., spherical) and does not migrate like a localization wire. Exemplary two- and three-dimensional shapes, such as rings, markers with legs, etc. are described herein.

The smart marker can be self-centering in the tissue or cavity of interest so that when accessed by the apparatus of the present invention the user is assured that the smart marker is located at or can otherwise indicate the volumetric center of the tissue or cavity of interest.

The smart marker desirably is capable of deployment by a variety of percutaneous delivery devices such as device 2160 shown in Figure 14, or through any of the delivery devices described herein. This device is typically a cannula or similar instrument, typically made of surgical grade stainless steel, having a lumen capable of receiving and delivering the smart marker 2100 to the site of interest through a sharpened distal end by a pusher, syringe, or like device as shown in Figure 14. The smart marker should be capable of being deployed under a variety of guidance techniques as known by those of skill in the art, such as regular mammography, stereotactic imaging, fluoroscopy, magnetic resonance imaging, ultrasound, etc.

In addition to or as an alternative to being capable of remote detection, the smart marker 2100 is also capable of acting as or being a sensor, such as the proximity sensor described below. In other words, a sensor can be implanted into the tissue which is capable of detecting the presence of another object within or outside the patient's body. In this arrangement, feedback apparatus for reading any output from such sensor to accomplish the goals of this invention are also contemplated. For instance, smart marker 2100 can transmit electromagnetic, optical, ultrasonic, or other information via a battery or other power source, or may be capable of recording information remotely or internally that can be detected by another device.

Finally, the smart marker desirably is capable of remote detection via one or more techniques, singly or in combination, such as ultrasonic, thermal (e.g., infrared), optical, magnetic, fluoroscopic, radiographic, inductance, and the like. Preferably, however, the smart marker is at least partially magnetic so that it may be detected via the preferred magnetoresistive techniques described in detail below.

Another variation of the smart marker may include a reflective implantable bead that returns a unique signature when exposed to an ultrasound source or other radio wave source. For example, the bead could be ultrasonically reflective and emit a distinct signature when exposed to ultrasonic energy. Also, the bead may be an active micro-machine that produces a unique signature in response to external excitation, e.g., magnetic excitation.

Tissue Modification Device

Figure 15 shows an exemplary tissue modification system 2200 (without smart marker 2100) comprising a tissue modifying device 2300, communication protocol interface 2400, radio frequency (RF) generator 2500, computer 2600, and feedback device 2700.

In this particular configuration, tissue modification device 2300 is a surgical cutting instrument. The manner in which the tissue is removed is not particularly critical to the invention. This cutter may take the form of, for example, a mechanical cutter utilizing a blade or the like such as a scalpel, a laser or other optical energy device, an ultrasonic energy device, an RF energy device, a microwave energy or other electrical device, or any other medically useful cutting instrument.

One example of a surgical cutting device suitable for combining with a sensor is a Bovie. A Bovie is a commercially available instrument used for electrosurgical dissection and hemostasis. The term "Bovie" commonly refers to a monopolar electrosurgical device that was developed nearly seventy years ago by William T. Bovie. This early device, described in U.S. Pat. No. 1,813,902, has met with acceptance over the years within the surgical community to the extent that current versions are referred to as a "Bovie". The use of the term Bovie is intended to include console/generator Bovies as well as handpiece/instrument variations. The use of the term Bovie is intended to include monopolar and bipolar variations.

Such devices typically consist of a handle 2320 having a first or "active" electrode 2340 extending from one end. The other end of the handle is electrically coupled via a transmission cable 2360 to an RF generator 2500 shown in Figure 15 which provides a high frequency electric current in, for instance, either an alternating current (AC) cutting mode or a pulsed coagulating mode. A remote control switch (not shown) typically is attached to

the generator and commonly is present as a foot switch located near the user, or as a hand switch on the Bovie. During a biopsy procedure, a second or "return" electrode (not shown), having a much larger surface area than the active electrode, will be positioned in contact with the skin of the patient. To cut, coagulate, or remove tissue by ablation, the surgeon brings the active electrode 2340 close to the tissue to be cut or coagulated. This is a starting condition where the instrument has not touched tissue. At this point in time, the electrical switch is activated whereupon the active electrode 2340 is brought into close proximity with the tissue to be cut. Electrical current then arcs from the active electrode 2340 and flows through tissue to the larger return electrode. In a cutting mode, the electrical arcing and corresponding current flow results in a highly intense but localized heating which causes cell destruction and tissue severance. Following a short cutting routine, the instrument again is elevated in still air away from the tissue for two or three seconds. In general, the device can be switched to a pulsed, higher voltage input to perform in a coagulating mode. These principles are well known to those skilled in the art of electrosurgery.

Given the multifaceted nature of the Bovie device described above, it is clear that device 2300 may take on any number of forms so to modify tissue according to the present invention. For instance, we use the terms "modify" and "modification" in this context to mean using RF or other electromagnetic energy to ablate or coagulate as described above (or by specific biopsy techniques known in the art, such as coring, aspiration, and the like), using mechanical energy such as cutting with a knife edge, etc.

Also, the invention may include using a needle to inject a migratory dye, contrast agent, or Tc (technecium) to locate a sentinel node, using a needle to inject a radiopharmaceutical or chermotherapeutic agent, using a needle to inject lidocaine or other local anesthetic in preparation for a lumpectomy, etc.

Furthermore, although not shown, tissue modification device 2300 may further be capable of removing or retrieving tissue. This is particularly important if the device 2300 is used as described above in an ablation mode; it is even more important if the device is used in a cutting mode. For instance, when a suspect tissue region, lesion, calcification, or the like is approached by device 2300 via cutting or ablation, it is often necessary for the suspect tissue to be dissected and removed from the patient. This can be accomplished via careful use of the active electrode 2340 to excise the suspect tissue, or an additional cutting

device may be fitted on the tissue modification device 2300 so that the tissue can be excised. In addition, once so excised, the tissue is then removed from the healthy tissue. Removal may be accomplished using forceps, grasping tools, vacuum-assisted tools and the like (not shown). Of course, the particular tissue removal device of interest will depend upon the type and size of the tissue to be removed, the portion of the body from which the tissue is to be removed, etc.

Proximity Sensor

In order for the invention to be capable of sensing the proximity of the remotely detectable smart marker to the device 2300, the tissue modification device is equipped with one or more proximity sensors 2380 as shown in Figure 15 and as described below.

By "proximity", we mean the instantaneous or average distance between the smart marker (e.g., 2100) and the sensor (e.g., 2380) or to a defined reference point inside or outside the body of the patient. It also means an instantaneous or average location of the smart marker with respect to the sensor or to another defined reference point within or outside the patient's body. Such distance and location information may be determined and displayed in one, two, or three-dimensional form using Cartesian, polar, or other coordinates. In broader terms, "proximity" can be thought of in the context of this invention to mean any information regarding the location of another object, including the remotely detectable smart marker, relative to the sensor or sensors or to any predetermined point or object.

Sensor 2380 may be a number of sensors capable of detecting the location of and distance relative to smart marker 2100.

An example of a proximity sensor 2380 includes a contactless magnetoresistive (MR) sensor that is generally considered together with interface 2400 as will be discussed below. Such a sensor is typically made up of thin strips of permalloy (NiFe magnetic film) whose electrical resistance varies with a change in applied magnetic field. It is capable of detecting the change in the ambient magnetic field due to the presence of a magnetic object, such as that superimposed by a magnetic smart marker 2100. We have found that a digital MR sensor or magnetometer such as the three-axis HMC2003 manufactured and sold by Honeywell, Inc. is particularly suitable for this invention.

This particular MR sensor detects the strength and direction of the change in the ambient magnetic field and uses triangulation techniques to communicate the x, y, and z components of the magnetic smart marker directly to a computer as a digital output signal. It has a resolution of 70 μGauss and field range of ± 2 Gauss, which is suitable for the applications required by the present invention. Other HMC MR sensors sold by Honeywell, Inc. are suitable as well.

Another variation of the invention includes using a magnetic, alternating current (AC), radio-frequency, or ultrasound source to produce a field to "illuminate" the surgical area. The generated field may cause a smart marker to produce a signal for detection by sensors. For example, if the generated field is an AC field, the sensor may distinguish the generated AC magnetic field from the earth's magnetic field. Once "illuminated" by the AC field, the marker may then induce a current which can be used to generate a particular signal for the sensor to determine the location of the marker.

In another variation, the source may be configured to produce a field over a range of frequencies and a particular smart marker can be configured to produce a signal upon exposure to a particular frequency. Therefore, the frequency specific marker can be distinguished from a second smart marker that is configured to produce a signal upon exposure to a second frequency. For example, in the case of ultrasound, a field may be transmitted over a range of frequencies. Upon exposure to its triggering frequency, the marker may emit a "response" frequency for its signal. In such a case, the sensors will detect the increased gain in the "response" frequency. The smart markers may be configures such that the "response" frequency is or is not unique to each smart marker. The above variation allows for discrete positioning of numerous markers wherein each smart marker may be distinguished from another smart marker.

As shown in the example of Figure 15, proximity sensor 2380 is located on the Bovie device 2300 near the active electrode 2340. In this particular embodiment, communication protocol interface 2400 is connected to sensor 2380 via data transmission cable 2370. Here, interface 2400 is considered part of the proximity sensor 2380 in the sense that it includes a microprocessor, logic devices and other hardware, and embedded software to accomplish the various features of the sensor 2380. Interface 2400 typically determines such measurement parameters as the data sample rate, zero offset, output format, and averaging. The sensor 2390 is discussed separately from interface 2400 for

purposes of this invention since a configuration as is shown in Figure 15 better serves the purposes of the invention.

Although the preceding discussion of the proximity sensor of the present invention is in the context of a MR sensor, the sensor can also be of other types, such as inductance, radioactive, thermal, optical, Hall effect, etc. However, magnetic sensors, and especially magnetoresistive sensors, are preferred due to their sensitivity as proximity sensors, their availability as a commercial off-the-shelf digital component, and their compact size and geometry.

It is also within the scope of this invention that the tissue modification system 2200 comprise a fixed reference point, such as a magnet or like device, in combination with first and second proximity sensors together with means for determining the distance between these two sensors through information regarding the fixed reference point.

For instance, a computer-based mapping system used for endocardial mapping known as the CARTO system, by Bioscience Webster, a Johnson & Johnson Company, may be useful in the present invention. Here, a fixed reference point, such as a magnet, is placed outside the patient's body but in a relatively close location, such as underneath the operating table. A first proximity sensor, preferably disposed in or near the tissue or cavity of interest, is used to calibrate the system and record its spatial location relative to the fixed reference point. Having this information, a second proximity sensor, preferably but not necessarily disposed on the tissue modification device, is then utilized by this system to determine its location relative to the fixed reference point.

With this information from each sensor, the device can calculate the distance between the first and second proximity sensors and provide the user with feedback information to instantaneously guide the tissue modification device to the tissue or cavity of interest. The device can determine this distance via software connected to or programmed in the device, for instance.

Also, an external reference marker may be placed on the Bovie hand-piece to provide spatial locations of the hand-piece relative to the surgical site. This information is provided as another input to the system for triangulation.

A further variation of the invention includes implanting a smart marker of known size and having the ability or means, as described herein, to provide feedback regarding distance to a detector. The detector is placed on a Bovie or scalpel. Therefore, the

feedback from the smart marker is used to calculate the distance between the smart marker and the Bovie/scalpel.

From a clinical standpoint, two additional features may prove useful. First, the position of the Bovie/scalpel is located in three dimensional space by any commercial or proprietary positioning system capable of such real time detection and positioning. Also, in cases where the detector is not placed directly on a cutting edge of the Bovie/scalpel, the position of the cutting edge is located with respect to the sensor which measures the distance from the smart marker. The system is configured such that when the distance from the detector to the smart marker is indicated to be zero, the positioning system will indicate that the position of the cutting edge is equal to the position of the smart marker.

Second, the original target is located on two orthogonal x-ray views in which the smart marker is clearly visible. These two views are scaled and oriented on a visual device such as a computer screen or monitor. The visual device displays a target point representing the smart marker. On the films of the x-ray views, the area to be surgically excised is circled. By overlaying the x-ray films on the visual device, the surgeon is able to use a computer to virtually circle the smart marker in both views. Then, using a software tool (e.g., SolidWorks), a shell or envelope 2762 representing the volume to be surgically excised can be created around the virtual marker as illustrated in Figure 20.

As the surgeon approaches the smart marker with the Bovie/scalpel, the surgeon will know how close the Bovie/scalpel is to the shell or envelope 2762 by using the visual device, or any other method described herein. The result is a three dimensional electronic "cage" around the region to be excised thereby assuring the target will be excised.

The invention also has the ability to provide feedback, as described herein, to maintain a preset distance from the marker so that a predefined margin plus the volumetric lesion field may be excised.

Computer and Associated Software

As shown in Figure 15, the invention may optionally comprise a computer system 2600 to transform the information generated by the sensor 2380 through interface 2400 to drive a feedback device 2700 as will be described below. Note that the term computer is meant to include any type of computing device having a processing unit suitable for calculating and, preferably, displaying the route to the smart marker. The computer may variously be a dedicated computer capable only of displaying the location of the smart marker, a digital signal processor (DSP), or it may be a common multi-purpose programmable computer such as a personal computer or laptop. Also contemplated by the term computer is a device configured to perform the steps discussed below.

The invention typically includes a computer program on a computer-readable medium which transforms data produced by the sensor 2380 and interface 2400 into a desired form of output data which allows for real time feedback informing the user of the location and distance of the smart marker relative to the tissue modifying device.

Turning now to the example of the invention shown in Figure 15, computer 2600 is connected via a typical data port connection 2720 to interface 2400. The output of interface 2400 (and sensor 2380) includes the x, y, and z (or polar coordinate) positional data of interest. In the Honeywell HMR2300 device, this data is output in the form of three 16-bit values at a rate of either 10 or 154 Hz via an RS-232 or RS-485 unit. This interface protocol is clearly exemplary and is described herein for purposes of illustration as one technique for transmitting the positional data of interest to a computer or other device.

As schematically depicted in Figure 15, once this positional data arrives at computer 2600, it is directed by a set of instructions (represented here by interface module 2800) to temporary memory means such as a buffer or RAM (not shown). This temporary memory means can also used for storing various important user input data, smart marker parameters, and calibration data.

After the various calibrations are performed (discussed below), the software instructs the microprocessor at step 2860 to transform the positional data into a form adequate for driving the feedback device 2700. Module 2860 can also represent the processing required to calibrate and zero the device as described below.

Once this data is manipulated at step 2860, the software then interfaces with feedback device 2700 through feedback device driver module 2880. Module 2880 is

configured to drive the display as shown in Figures 17 and 18, in which each of the three instantaneous positional data points is transformed for a user to interpret.

In essence, though, the computer is used simply to calculate and display the relationship between the cutting or tissue modification device and the smart marker. Any control or calculating device suitable for this service is acceptable. Indeed, where this invention is used as a portion of a robotic device, e.g., where the actor who removes the tissue is not a human surgeon but a robotic surgeon, the display is not critical. An appropriate feedback relationship between the robot and the sensor is more suitable.

Note the example of Figure 17, which has a two-dimensional graphical representation 2720 of the relative position of the smart marker in the x-y plane and an alphanumeric display 2740 to represent the distance of the sensor to the smart marker in the z plane. This is an example of a display and feedback device. Such a device may embody any number of display configurations, such as the three-dimensional graphic 2760 shown in Figure 18.

Although Figure 15 depicts the interface 2400, feedback device 2700, and computer 2600 as three separate devices, it is within the scope of the invention for each of these elements to be consolidated into two units or even a single unit. It may also comprise additional units as needed. As long as the basic functions described herein are accomplished, any system 2200 architecture other than the one shown in Figure 15 is sufficient.

Feedback Device

Another component of the invention used with the manually operated tissue modification unit is a feedback device that provides delayed, recorded, or, preferably, instantaneous information as to the location and distance of the remotely detectable smart marker relative to the position of the sensor or another point. This enables the user to direct the tissue modification device to a location of a detectable smart marker and surgically remove a lesion identified by the smart marker.

For instance, the feedback device can be as simple as digital display 2390 located on the body of device 2300 and shown in Figures 15 and 19. This display 2390 can present data such as the distance of sensor 2380 from the smart marker 2100, the spatial location of sensor 2380 in the form of x, y, and z coordinates relative to a fixed reference point, etc.

Alternatively, or in addition to display 2390, any number of different feedback devices can be used with the invention. This is generically shown in Figure 15 as feedback device 2700.

For instance, the feedback device can be a visual display such as a cathode ray tube (CRT) or flat-screen monitor 2700 as shown in Figure 18. A visual display can present graphical information in real-time, such as the three-dimensional display 2760 in Figure 18 or the Figure 17 two-dimensional graphic screen 2720 combined with an alphanumeric readout 2740.

The visual display feedback device can be as simple as a numerical paper printout, a flashing light or combination of flashing lights and other information. It can also be as sophisticated as a virtual reality (VR) interface. VR displays are particularly well-suited for remote tissue manipulation, such as may be useful in a small community hospital where a surgeon may not have the ability to be physically next to a patient in need.

In broader terms, the user feedback device may be any device that provides information to the user regarding the distance and location data of interest. For instance, the feedback device can be an audio device which, singly or in combination with a visual or other type of feedback system, provides an audible signal to the user, such as tones of different frequencies, a series of variably timed "beeps" to indicate the relative proximity of the sensor to the smart marker, a computer-generated voice, etc.

Such a feedback device may also be, singly or in combination with any of the aforementioned devices, tactile or vibratory so that device 2300 transmits valuable proximity information directly to the hands of the user. Obviously, the transmission of information is provided in such a way that the user obtains feedback without affecting the operation of the cutting device. For instance, the device 2300 can be configured to vibrate at a given frequency correlating to the distance of the device from the smart marker such that the frequency increases as the device 2300 is moved closer to the smart marker. Of course, such a feature would optimally be used in combination with audio or visual feedback devices as well.

Method of Use

A remotely detectable smart marker is usually inserted into a mass of tissue either surgically or through a minimally invasive procedure using such devices as a biopsy

device, catheter, introducer, needle applicator, or similar device 2160 as shown in Figure 14. The marker preferably comprises a bio-inert capsule with ferromagnetic materials located within the capsule. Additionally, the smart marker may be surrounded by a resorbable filler body. The filler body may assist in preventing the smart marker from migrating, it may provide hemostasis, or it may provide other beneficial functions. The smart marker is preferably placed in a substantially volumetric center of a lesion. The smart marker could also be placed outside the lesion by a known value so as to not disturb the lesion.

Note that because the smart marker so implanted does not utilize a traditional wire, the patient has the freedom to enjoy a substantial delay of time between the implantation of the smart marker and the biopsy or lumpectomy procedure - enough so that she may even leave the hospital for a day or longer.

Prior to modifying the tissue, it is important that the system 2200 be properly set up and calibrated so that accurate positional data from the sensor 2390 and interface 2400 are relayed to the user.

It may be advantageous to first or continuously perform a zero-offset operation either through the software embedded in the sensor 2390 and interface 2400, or via the software discussed above and shown in Figure 16. The purpose of this step is to eliminate the effect of any specious magnetic or other field in the operating room or facility where the tissue modification is to be performed. Any field produced by other magnetic objects by local electromagnetic fields, or other field source will be detected to some degree by the sensor 2390. This compensation or zero offset step should obviously be accomplished in the vicinity of the operating theater or area in which the tissue manipulation procedure is to be performed so that any reading taken is relevant to the procedure at hand.

Once the exemplified system 2200 shown in Figure 15 is powered up and the ambient field strength is measured by sensor 2390, the user will know to offset this reading by pushing the "zero" button (as shown in Figure 17 in the "Initialize Room" section of the display). Alternatively, the user can be prompted on a display screen to do the same. Such a procedure can also be automatically performed by the software without the need for user input.

Once the ambient room magnetic or other field readings are "zeroed", the relative strength of the smart marker may be typically determined so that the system can be

calibrated. For instance, if the smart marker has been embedded in a woman's breast, it may be located just underneath the surface of the skin or it may be located several inches within the breast tissue. These variations and differences in the size of the breast will be present for nearly every use of the device. Therefore, for this variation of the inventive system, the surgeon-user must know the relative field strength of the implanted magnetic smart marker 2100 so that accurate positional data can be generated.

Typically, this is accomplished when the smart marker 2100 is manufactured. Ideally, a smart marker magnet should arrive from the manufacturer accompanied by data (in bar-coded or other computer-readable form) listing the various parameters necessary to calibrate the system 2200 for use with that particular smart marker.

If for some reason such data is not present and the system requires such information, the radiologist or technician implanting the smart marker prior to the use of the invention can obtain this calibration data themselves. Using, for example, a device similar to system 2200, the sensor 2390 (or active electrode tip 2340) is brought into contact with the smart marker 2100 and the system is placed into a mode where the field strength of the smart marker at this position can be read from a display or feedback device. The software can instruct the user to push a button to enter this initial field strength data into temporary data storage means, or a series of prompts (visual, audio or both) can be written into the software in an automatic calibration sequence to indicate to the user when the data has been entered into the temporary storage means by the computer.

In any event, the user is next prompted to move the sensor 2390 a predetermined distance, preferably along a single axis, away from the smart marker 2100. A similar field strength reading is taken by the sensor 2390 and interface 2400, and the data are similarly stored in temporary memory. The difference in these two values represents the field strength along the predetermined distance. It should be clear that the predetermined distance, or "working distance", should be at least the thickness of the patient's breast (if the smart marker is so implanted) or, in more general terms, the distance beneath the skin which the user expects the smart marker 2100 to exist. Preferably, this working distance is several inches longer.

Because the relationship between linear distance and magnetic field strength is a logarithmic one, the software preferably is configured to calibrate the system 2200 for that

particular smart marker so that the distance from the smart marker to the sensor 2390 can be accurately displayed in units of distance.

Once the smart marker has been placed in the tissue to be modified, the ambient field strength has been compensated for, and the sensor 2390 is calibrated, the device is ready for operation.

For purpose of example, the method of use described below is directed to performing a breast biopsy to obtain a tissue sample into which a smart marker has been deployed. The tissue manipulation to be described is monopolar RF cutting of tissue using the Bovie described above and shown as device 2300 in Figure 15. See Figure 19 for a depiction of the use of the present invention according to the description below.

The user, typically a surgeon, will already have general information regarding the location of the tissue to be excised and the location of the smart marker 2100. In the method shown in Figure 19, the tissue 2900 for excision is located directly below the nipple and areola 2920 so that the most direct approach is the most attractive one: a circumareolar incision. This minimizes the appearance of scarring and is therefore also a cosmetically desirable route to smart marker 2100.

The surgeon will then scan the surface of the breast in the region generally desirable for the incision, paying heed to the feedback means, such as the display in Figures 17 or 19, to determine the point on the surface of the breast closest to the smart marker.

The surgeon then energizes the active electrode tip 2340 via a foot pedal, or hand control switch (not shown) from RF generator 2500, and begins the incision 2940 towards the smart marker. During this process, the feedback device 2700 is instantaneously transmitting position and location information to the surgeon so that the surgeon can guide the instrument 2300 in the most direct path possible to the smart marker.

Once the surgeon has arrived in the vicinity of the smart marker so that it is either physically visible or so that it is time for a margin to be formed, the surgeon may continue cutting through the tissue to remove the desired volume of tissue (which is desirably marked in its volumetric center by smart marker 2100) and remove the biopsy sample, or the surgeon may use a special excision tool to do the same. All or a portion of the suspect tissue, lesion, calcification, or the like may be taken from the breast.

Note that the surgeon may remove the smart marker with the biopsy tissue sample, or choose to leave the smart marker in the remaining cavity for future examination should that be necessary.

It should be understood that although this device is described for use in assisting a surgeon in breast biopsy procedures, the device of this invention can be used in any application where tissue is to be manipulated and a smart marker is used to direct the user while manipulating that tissue. It is not limited to the breast, and the invention may be practiced be used in any portion of the body that can benefit from its application.

This invention has been described and specific examples of the invention have been portrayed. The use of those specific examples is not intended to limit the invention in any way. Additionally, to the extent that there are variations of the invention which are within the spirit of the disclosure and yet are equivalent to the inventions found in the claims, it is our intent that those claims cover those variations as well.

Cavity Marking Device and Methods for the same:

Figures 1A-1Q show various configurations of a preferred subcutaneous cavity marking device of the present invention. Here the marking device 100 is displayed as having either a generally spherical body 102 (Figure 1A), a generally cylindrical body 104 (Figure 1B), or a multi-faced or irregular body 106 (Figure 1C). In general, it is within the scope of this invention for the body to assume a variety of shapes. For example, the body may be constructed to have substantially curved surfaces, such as the preferred spherical 102 and cylindrical 104 bodies of Figures 1A and 1B, respectively. The body may have conical or ellipsoidal, etc. shapes as well. It is further within the scope of this invention for the body to have substantially planar surfaces, such as polyhedric (i.e. cubic, tetrahedral, etc.) or prismatic, etc. forms. Finally, the body may also have an irregular or random shape, in the case of a gel, combining features of various curved and planar surfaces. Body 106 of Figure 1C is an example of such an irregular body shape. The particular body shape will be chosen to best match to the biopsy cavity in which the device is placed. However, it is also contemplated that the body shape can be chosen to be considerably larger than the cavity. Therefore, expansion of the device will provide a significant resistance against the walls of the cavity. Moreover, the aspect ratio of the device is not limited to what is

displayed in the figures. For example, the cylindrical body 104 may have a shorter or longer length as required.

It is intended that the cavity marking device described herein may incorporate features of the smart marker also described herein. Alternatively, the cavity marking device may actually use the smart marker within the body of the cavity marking device. The resulting variation yields a "smart" cavity marking device with features and benefits as described herein.

In the bodies of Figures 1A and 1C, the generally spherical marker 150 is located at or near the geometric center of the body. Such a configuration will aid the physician in determining the exact location of the biopsy cavity, even after the body degrades and is absorbed into the human or mammalian body.

The ring-shaped markers 154 of Figure 1B are generally aligned along the longitudinal axis 114 of body 104. Note that although the ring-shaped markers 154 are spatially oriented so that their longitudinal axes lie along the longitudinal axis 114 of the body 104, each marker may assume a wide variety of random or predetermined spatial orientations other than the aligned orientation seen in Figure 1C. It can be appreciated that a nonspherical marker such as marker 154 is useful in aiding a physician in determining the spatial orientation of the deployed inventive device.

Obviously, markers 150 and 154 may reside in locations other than those demonstrated in Figures 1A-1C. It is, however, preferred that markers 150 and 154 dwell in a predetermined, preferably central, location and orientation in the device body so to aid the physician in determining the location and orientation of the biopsy cavity. The markers herein described may be affixed to the interior or on the surface of the body by any number of suitable methods. For instance, the marker may be merely suspended in the interior of the body (especially in the case where the body is a gel), it may be woven into the body (especially in the case where the marker is a wire or suture), it may be press fit onto the body (especially in the case where the marker is a ring or band), or it may affixed to the body by a biocompatible adhesive. Any suitable means to affix or suspend the marker into the body in the preferred location is within the scope of the present invention.

Tissue regrowth in a particular orientation can also be promoted by a body design shown in Figure 1D. Here, body 110 contains a number of pores 138 through which tissue may grow. The pores may also be aligned in a substantially parallel fashion, traversing the

thickness of the body so that tissue may regrow from one side of the body through to the other side. This is demonstrated in inset Figure 1E, which shows a portion 130 of Figure 1D in partial longitudinal cross section, complete with pores 138 traversing through the thickness of portion 130. Such pores 138 can be parallel to each other as shown in Figure 1E, or they may be perpendicularly, radially, or even randomly oriented in the device body.

A trio of markers is also shown in Figure 1D evenly aligned along the body longitudinal axis 140. Barb marker 156, spherical marker 150, and ring-shaped marker 154 demonstrate the use of different multiple markers in a single body 110. As previously described, such a design helps a physician to determine the spatial orientation of the inventive device when it is deployed in a biopsy cavity. Although the barb marker 156 is illustrated in a 'V' configuration, it is an important aspect of the barb marker 156 to have a shape that is clearly not spherical. This allows the barb marker 156 to be easily distinguished from calcifications that may be observed during any noninvasive imaging techniques.

Figure 1F depicts a further embodiment of the present invention in which body 112 is enveloped in an outer shell 142 consisting of a layer of bioabsorbable material such those mentioned above. This configuration allows the perimeter of the biopsy cavity to be marked to avoid exposing the cavity, in the case of a "dirty" margin where re-excision may be necessary, to remaining cancerous cells as the tissue begins to re-grow into the cavity. Such a shell 142 can be radiopaque and/or echogenic *in situ*, or it may be augmented with an additional coating of an echogenic and/or radiopaque material. The shell 142 can also be made to be palpable so that the physician or patient can be further aided in determining the location and integrity of the implanted inventive device.

Shell 142 may be designed to have a varying bioabsorption rate depending upon the thickness and type of material making up the shell 142. In general, the shell can be designed to degrade over a period ranging from as long as a year or more to as little as several months, weeks, or even days. It is preferred that such a bioabsorbable shell be designed to degrade between two and six months; especially preferred is three months. In the design of Figure 1F, interior 144 of body 112 may be a cross-linked, collagenous material that is readily absorbed by the human or mammalian body once the shell 142 degrades. Interior 144 may be filled with a solid or gelatinous material that can be optionally made radiopaque by any number of techniques herein described.

As will be described in additional detail with respect to Figures 2A-2F, marker 150 in the device shown in Figure 1F may be permanently radiopaque or echogenic, or it may be bioabsorbable and optionally coated with a radiopaque and/or echogenic coating that degrades over a predetermined period of time. It is clinically important that the marker remain detectable for at least about one to five years so that the physician may follow the patient to ensure the health of the tissue in the vicinity of the biopsy cavity. Especially preferable is a marker whose radiopacity or echogenicity lasts between about one and three years.

Each of the bodies depicted in Figures 1A-1F may be made from a wide variety of solid, liquid, aerosol-spray, powder, spongy, or expanding gelatinous bioabsorbable materials such as collagen, cross-linked collagen, regenerated cellulose, synthetic polymers, synthetic proteins, and combinations thereof. Also contemplated is a body made from a fibrin-collagen matrix, which further prevents unnecessary bleeding, and minimizes the possibility of hematoma formation.

Examples of synthetic bioabsorbable polymers that may be used for the body of the device are polyglycolide, or polyglycolic acid (PGA), polylactide, or polylactic acid (PLA), poly ε-caprolactone, polydioxanone, polylactide-co-glycolide, block or random copolymers of PGA and PLA, and other commercial bioabsorbable medical polymers. Preferred is spongy collagen or cellulose. As mentioned above, materials such as hemostatic and pain-killing substances may be incorporated into the body and marker of the cavity marking device. The use of hemostasis-promoting agents provides an obvious benefit, as the device not only marks the site of the biopsy cavity but aids in healing the cavity as well. Furthermore, such agents help to avoid hematomas. These hemostatic agents may include AVITENE Microfibrillar Collagen Hemostat; ACTIFOAM collagen sponge, sold by C. R. Bard Inc.; Kensey Nash collagen sponge; GELFOAM Sterile Powder or Sponge, manufactured by The Upjohn Company (Michigan); SURGICEL Fibrillar from Ethicon Endosurgery, Inc.; TISSEEL VH, a surgical fibrin sealant sold by Baxter Healthcare Corp.; Helistat collagen sponge from Integra Lifesciences; Helitene absorbable collagen hemostatic agent in Fibrillar form; and polyethylene glycol (PEG) or collagen/PEG compositions from Cohesion. Such agents also have the useful property of expanding between 3 and 30 times their compressed volume upon release into a cavity and/or upon hydration.

The device may also be made to emit therapeutic radiation to preferentially treat any suspect tissue remaining in or around the margin of the biopsy cavity. While it is within the scope of this invention that either or both of the marker or markers and the bioabsorbable body may be radioactive, it is envisioned that the marker would be the best vehicle for dispensing such local radiation treatment or similar therapy. In another variation, the body of the cavity marking device may temporarily accommodate a radiopharmaceutical. For example, the body may comprise a bioabsorbable element such as collagen having an opening for placing a nonabsorbable balloon through a cannula into the opening; the balloon is then filled with a radioactive fluid and after a suitable time, emptied and removed. Additionally or alternatively, the balloon may be removably located within the collagen prior to implantation of the marking device in the cavity; the balloon then may be filled with a radioactive fluid, using a needle to access the balloon, then after a suitable time, emptied, then removed. In either case, it is preferable that the collagen become hydrated prior to filling the balloon with the radioactive fluid to allow the collagen to be pushed outwardly with the force of the balloon expanding. Alternatively, the bioabsorbable body may include preformed channels through which radioactive seeds can be placed and directed to the appropriate location. These channels would provide precise placement of the radioactive seeds for optimum therapy. The seeds may have a rapid decay or low dose to allow for permanent implant; alternatively, the seeds may be tethered for ease of removal following therapy.

Also, the body itself may be adapted to have radiopaque, echogenic, or other characteristics that allow the body to be located by noninvasive technique without the use of a marker. Such characteristics permit the possibility of locating and substantially identifying the cavity periphery after deployment but prior to absorption of the device. Such an embodiment may allow delivery in liquid or gel form through a much smaller lumen than those marking devices having one of the markers previously described. Furthermore, an echogenic coating may be placed over the radiopaque marker to increase the accuracy of locating the marker during ultrasound imaging.

Further, as illustrated in Figures 1G-1K, the device can be deployed as a loosely wound ball or looped arrangement of bioabsorbable surgical material with a marker placed at the geometric center of the device. The material may be, for example, resilient suture material, that upon deployment into a tissue cavity provides resistance against the cavity

wall and allows the marker to be located at substantially the center of the cavity. In this variation, suture material may be looped through the band/ring 154; in such a configuration, the suture material acts as the body of the inventive device. As described elsewhere, the suture may comprise a bioabsorbable material. The suture material may also have radiopaque, echogenic, or other characteristics described herein that aid in the noninvasive location of the device. Desirably, the suture material 158 is flexible to facilitate the expansion of the filler body to fill the cavity. The device may be in the form of multiple passes of suture material 158 looped through a marker 154 (Figure 1G). The suture material may also be configured in the form a pair of opposing loops 160 with a marker 154 between the loops 160 (Figure 1H), or two pairs of opposing loops 160 with the marker 154 in the center of the device (Figure 1I). The opposing loops 160 may be bent longitudinally to form opposing members 162 (Figures 1J, 1K). The longitudinally bent opposing member 162 may be, but is not necessarily, formed by applying heat to the suture to set the "bend". An aspect of this variation is that the opposing members 162 provide resistance against the walls of a delivery device, thereby, minimizing the possibility of the marking device being prematurely released from the delivery device. Upon the desired deployment, the resiliency of the suture will expand the device and provide significant resistance against the walls of the cavity with the opposing members 162 providing additional resistance. It is within the scope of this invention to optionally deliver a biocompatible liquid, gel, powder, or the like before, during, or after deployment of a self-centering suture-containing device such as those illustrated in Figures 1G-1K.

Figures 1L and 1M illustrate preferred embodiments of the inventive tissue cavity marking device 182 and 184 each having an elongated body 178 or 180 with a circular or rectangular cross section and a metallic marker band 154. The metallic marker band 154 preferably is oriented with its axis 174 perpendicular to the long axis 176 of the body 178 or 180 to allow maximum compression of the elongated body in the radial direction. The elongated bodies 178 and 180 preferably comprise collagen-containing material with hemostasis-promoting properties.

Figures 1N and 1O illustrate embodiments of the inventive tissue cavity marking device 186 and 188 each having an elongated body 190, 194 with a circular or rectangular cross section and a marker 192, 196 attached about the elongated body 190, 194. One method of making the circular bodies 190 and 178 of marking devices 186 and 182 is to

start with a rectangular cross section piece of collagen about 0.5 inches long x 0.2 inches wide x 0.2 inches deep and compress it by squeezing and/or rolling it to form a circular cross section body about 0.5 inches long x 0.1 inches diameter. In another variation, body has a length of between about 0.3 and about 0.5 inches, a compressed width or diameter of about 0.05 inches to about 0.1 inches, and an uncompressed width of about 0.15 to about 0.25 inches. The dimensions may vary however, dimensions may be selected so that the cavity marking device may be delivered with a biopsy device such as a Mammotome (e.g., 11GA, 14GA, etc.). The marker may be a band or ring, split ring, or any other type of marker described herein. For example, although the marker is illustrated as circular, it may alternatively be rectangular or C-shaped. It is contemplated that the marker 192, 196 may be, for example, press fit or crimped about the body 192, 196. A C-shaped ring may be positioned on the elongated body, then crimped, either to partially close the C to lock it in place while still providing orientation or to fully close it to form a ring. Alternatively, the marker may comprise a $BaSO_4$-loaded silicone rubber band or the like that may be stretched over the body and held in place by a friction fit. Alternatively or additionally, an adhesive (not shown) may be used to secure placement of a marker about a body. A further variation of the embodiment described above includes a marker having a length as measured by 198 of figure 1N of approximately 0.030 inches (0.8 mm) and a dimension of approximately 0.095 inches (2.4 mm) as measured in a direction perpendicular to the length. But the dimensions may be varied as needed for the application. For a circular marker, this dimension is the outer diameter.

Figure 1P illustrates an embodiment 200 of the invention having markers 201 deposited along a body consisting of a thread-like material 202. The markers 201 may be clustered in groups as shown or may be situated along the entire length of the body. The markers 201 are remotely detectable as described herein and are deposited by any method such as, for example, painting, coating, dipping, spraying, or co-extruding. Another variation of the invention includes a device having a body comprising a thread-like material 202 where the entire body is remotely detectable as described herein. In such a variation, the invention may also include a delivery means for delivering the detectable material in a thread-like configuration. For example, the delivery means may include a delivery nozzle with a hydraulic source, a pump, a syringe, a tube and plunger combination, or any other

device that delivers the detectable material in a thread-like configuration into a biopsy cavity.

Figure 1Q illustrates another embodiment 204 of the invention having a body 206 with a marker 208 serving as an outer layer. One variation of this embodiment includes a balloon-type material 208 that is detectable as described herein and that adheres to the margin of the cavity. The balloon material 208 may be filled with a biodegradable body 206. As the body 206 degrades, the balloon material 206 remains adhered to the margin of the cavity. The balloon material may include an adhesive on an exterior surface to assist the balloon material 208 in adhering to the margin of the cavity. An adhesive may be formed with carbon or other directly visible material, or with radiopaque, echogenic, magnetic, or other remotely detectable material. The balloon material 208 may, for example, be porous, or may comprise an elastomer optionally with a radiopaque material such as powdered tantalum or tungsten, barium sulfate, barium oxide, or other barium radiopaque substance. For example, the balloon material may be a silicone rubber or a $BaSO_4$ loaded silicone rubber. The body 206 may comprise a bioabsorbable liquid. In another variation, a collagen ball may be used as the body 206. The outer shell 208 may comprise a tissue adhesive with radiopaque, ultrasonic, echogenic, magnetic, or other remotely detectable properties.

In one method of making the marking device 182 or 184, a marker 154 (or any other marker) may be placed on the edge of a sheet of filler body material such as gelatin or collagen. The sheet may then be rolled or folded to form a device having an elongated body 178 or 180 having a circular or rectangular cross section. Alternatively, a block of collagen or other filler body material may be cut into a rectangular or cylindrical shape. A needle may be used to create a hole through one end lengthwise, preferably only halfway through. A tube containing a marker such as marker 154 may be placed into the hole created by the needle, and a plunger used to push the marker out of the tube and into the filler body, where it may be held in place by friction. Multiple markers may be used to help provide orientation when visualized in the patient on X ray, ultrasound, etc. The filler body may be rolled or compressed, either before or after placement of the marker, as needed for delivery to the tissue.

One advantage of the collagen material and some of the other materials disclosed herein for the body of the marking device is that it can be easily cut with scissors, a knife,

or a scalpel. Therefore, a physician can trim the body of the marking device to fit the cavity during the procedure. This is especially useful when creating the cavity and placing the marking device surgically. Furthermore, if re-excision in the same region is required, the surgeon will have no trouble cutting through the body of the marking device.

Figures 2A-2H illustrate various forms of the marker 110. The marker 110 may be a sphere 150 (Figure 2A), a hollow sphere 152 (Figure 2B), a ring or band 154 (Figure 2C), a split or "C-shaped" ring (Figure 2H), a barb 156 (Figure 2D), a flexible suture or flexible wire 158 (Figure 2E), or a crimped tube or a folded strip of material 172 (Figure 2G). Also, the marker may have a distinguishing mark 170 (Figure 2F). As mentioned above, the barb 156 is illustrated in Figure 2D as having a "V" shape. The barb 156 is intended to distinguish the marker from calcifications when viewed under noninvasive imaging techniques. As such, the barb 156 is not limited to the "V" shape; rather, it has a shape that is easily distinguishable from a spherical or oval calcification.

The marker itself may aid in deploying the body. The marker may be made of a spring material such as superelastic nickel titanium alloy or stainless spring steel for delivery in compression to expand the body to substantially fill the cavity. The barb 156 of Figure 2D and the flexible wire 158 of Figure 2E are particularly suited to mechanically aid deployment of the body (not shown).

The hollow sphere 152 of Figure 2B is more susceptible to detection by ultrasound than the solid sphere 150 of Figure 2A. For instance, such spherical markers such as markers 150 and 152 can be beads of silicon or silicon-containing compounds, such as silicone or SiO_2. In the case of a ring or band marker 154 seen in Figure 2C, the body of the cavity marking device may be woven or placed through the band or ring 154. The marker may also be a wire or suture 158 as shown in Figure 2E and as discussed in greater detail below. In such a case, the marker 158 may be affixed to the exterior perimeter of the body by an adhesive or woven through the body. Another improvement may arise from the marker wire or suture 158 being configured in a particular pattern within the body of the device, e.g., wrapping around the body in a helical manner. As described elsewhere, the wire or suture 158 may also be configured to comprise the body of the marking device. In the case of the marker 150 shown in Figure 2F, distinguishing or identifying mark 170 can be in the form of simple marks as shown, or it may be one or more numbers, letters, symbols, or combinations thereof. These marks 170 are preferably located in more than

one location on the marker 150 so that the marker may be readily and simply identified from multiple orientations under a variety of viewing conditions. Such a mark 170 can be used to identify the patient and her condition, provide information about the marker and body of the tissue cavity marking device, provide information about the circumstances and date of the implantation, who performed the procedure, where the procedure was performed, etc. In the case of multiple biopsy sites, this distinguishing mark 170 permits one to differentiate and identify each different site. The mark 170 may be applied via any number of techniques such as physical inscription, physical or plasma deposition, casting, adhesives, etc. The mark 170 may also be an electronic chip providing any necessary information in electronic form that can be remotely detected by appropriate means. The marking device may use the device or technology of a Trovan Transponder (Electronic Identification Systems--Santa Barbara, California). Medical information may itself be directly encoded into the device, or a code on the device may be keyed to a corresponding record in a computerized database containing the medical information. The medical information may include such data as a pathology report of a biopsy sample taken from the site being marked, and this information may be entered into the computer record before or after implantation of the marking device. Furthermore, this information may be updated as needed. Alternatively or additionally, the mark 170 may itself be remotely programmable to add patient or procedure information, pathology information, or the like after implantation in the body, although adding such capability to the marking device may increase its size.

An important aspect of the invention is that the marker may be radiopaque, echogenic, mammographic, etc. so that it can be located by noninvasive techniques. Such a feature can be an inherent property of the material used for the marker. Alternatively, a coating or the like can be added to the marker to render the marker detectable or to enhance its detectability. For radiopacity, the marker may be made of a nonbioabsorbable radiopaque material such as platinum, platinum-iridium, platinum-nickel, platinum-tungsten, gold, silver, rhodium, tungsten, tantalum, titanium, nickel, nickel-titanium, their alloys, and stainless steel or any combination of these metals. By mammographic we mean that the component described is visible under radiography or any other traditional or advanced mammography technique in which breast tissue is imaged.

As previously discussed, the marker can alternatively be made of or coated with a bioabsorbable material. In this case, the marker can, for instance, be made from an additive-loaded polymer. The additive is a radiopaque, echogenic, or other type of substance that allows for the noninvasive detection of the marker. In the case of radiopaque additives, elements such as barium- and bismuth-containing compounds, as well as particulate radiopaque fillers, e.g., powdered tantalum or tungsten, barium carbonate, bismuth oxide, barium sulfate, etc. are preferred. To aid in detection by ultrasound or similar imaging techniques, any component of the device may contain air bubbles or may be combined with an echogenic coating. One such coating is ECHO-COAT from STS Biopolymers. Such coatings contain echogenic features, which provide the coated item with an acoustically reflective interface and a large acoustical impedance differential. As stated above, an echogenic coating may be placed over a radiopaque marker to increase the accuracy of locating the marker during ultrasound imaging. Furthermore, in variation of the device which comprise a body of porous collagen or the like, the body may contain small pockets of air, As discussed elsewhere herein, these pockets of air may enhance the echogenic characteristics of the device allowing for detection using ultrasound. To prolong this period of ultrasound detection via use of the air pockets, it may be necessary to prevent immediate hydration of the body upon contact with bodily fluids. One means of prolonging this period is to coat the body with a biodegradable coating forming a shell that delays or even prevents hydration of the body of the device. For example, hydration may be delayed or prevented for about 2 weeks to about 2 months. Delaying hydration of the body of the device allows imaging to locate a site for purposes such as: injection of lidocaine in preparation for lumpectomy; targeting localized radiation therapy or chemotherapy; and injection of migratory dyes, contrast agents, and Tc for sentinel node identification, which is described in detail herein.

Note that the radiopacity and echogenicity described herein for the marker and the body are not mutually exclusive. It is within the scope of the present invention for the marker or the body to be radiopaque but not necessarily echogenic, and for the marker or the body to be echogenic but not necessarily radiopaque. It is also within the scope of the invention that the marker and the body are both capable of being simultaneously radiopaque and echogenic. For example, if a platinum ring marker were coated with an

echogenic coating, such a marker would be readily visible under x-ray and ultrasonic energy. A similar configuration can be envisioned for the body or for a body coating.

The marker is preferably large enough to be readily visible to the physician under x-ray or ultrasonic viewing, for example, yet be small enough to be able to be percutaneously deployed into the biopsy cavity and to not cause any difficulties with the patient. More specifically, the marker will not be large enough to be palpable or felt by the patient.

Another useful version of the invention is shown in Figure 3A. In this device, there are several cylindrical body members 302; however, there is no limit to the number of body members that can make up the device. The body members 302 can individually or together take on a variety of sizes and shapes as discussed above depending on the characteristics of the biopsy cavity to be filled. The body members 302 may uniformly or in combination be made of one or more materials suitable for use in a biopsy cavity as previously described.

Here one or more markers may traverse two or more body member segments through the interior of the body members 302 as shown in Figure 3A. Here, markers 318 are located substantially parallel to the longitudinal axis 320 of each right cylindrical body member 302 in their interior, connecting each body member 302 while marking their geometric center as between the markers. Such a marker 318 may be used in conjunction with the other markers as described above and may also be accompanied by one or more additional markers arranged randomly or in a predetermined pattern to variously mark particular sections of the device. Alternately, such a marker may, singly or in combination with other markers, be affixed on or near the surface of the sponge so as to mark the perimeter of the body member 302.

Of course, when used in conjunction with other connecting markers, marker 318 need not necessarily connect each body member; it may be used solely to indicate the orientation or location of each individual sponge or the entire device, depending on the material, geometry, size, orientation, etc. of marker 318. When not used in this connecting function, therefore, marker 318 need not traverse two body members 302 as shown in Figure 3A.

A variety of patterns can be envisioned in which all or part of the perimeter of the sponge body is marked. For example, a marker 322 can wrap around the body 302 in a helical pattern (Figure 3B), or it can be used in conjunction with other markers 324 in a pattern parallel to the longitudinal axis 320 of the body 302 (Figure 3C). Another useful

perimeter marking pattern is shown in Figure 3D, where marker segments 326 are affixed at or near the surface of the circular bases of the cylindrical body 302 in a cross pattern, indicating the ends of the sponge and their center. As seen from the figures, the marker(s) may, but do not necessarily, have some texture. Any marker pattern, internal or external to the body, is within the scope of the present invention. For the applications depicted in Figures 3A-3D, it is preferred that the marker be a radiopaque or echogenic wire or suture.

Another possible configuration is obtained by combining the suture or wire markers 158 in a body with any other type marker 150, 152, 154, or 156 or vice versa. For example, in Figure 3B, a spherical marker 150 may be placed in the center of the cylindrical body 302. Therefore, the cylindrical body 302 would contain the suture or wire marker 322 wrapped helically adjacent to the outer perimeter, and a marker 150 would be placed in the center of the cylindrical body 302. Such a combination may be obtained with any of the body and marker configurations as defined above.

Figure 3E illustrates another configuration where the marker 328 is helically or spirally wound and located within a body 302. Although not illustrated, the marker 328 may be placed within a channel (not shown) inside the body 302. The coiled marker 328 is more flexible than a straight wire and will have less tendency to migrate through the tissue than a straight wire might when body 302 is resorbed.

Figures 3F and 3G illustrate other cavity marking devices having a spirally or helically coiled marker 330 within (3G) or wrapped about (3F) a body 332. These devices are particularly suitable configurations for use in fine needle aspiration or small core biopsy. They can be configured to fit through a 20 to 18 gage needle such as a fine gage biopsy needle. They may be deployed from the distal end of an open-ended needle or through a side window. Coiled marker 330 is preferably made from fine gage radiopaque and/or echogenic wire, such as 0.003 to 0.005 inch PtIr, and preferably has an outer coil diameter of about 0.020 to 0.035 inches. The ends 331 of the coiled wire are preferably blunt and may even have balls 333 on the ends made, for example, by melting the ends of the wire or by dipping the ends in epoxy. Body 332 may be resilient, expanding when hydrated, as shown by the phantom line in Figures 3F and 3G. Alternatively, body 332 may simply function to support marker coil 330 for ease of insertion into the biopsy cavity, and may not expand appreciably when exposed to bodily fluids. Body 332 may contain or may be coated with an echogenic agent, and is preferably resorbable, leaving behind a very

flexible coil that may not necessarily maintain its helical shape following resorption of the body.

Figures 3H -3J illustrate cavity marking devices having a coiled marker 334, 338, or 340 within or wrapped about a body and partially extending from one end of the body 336. These configurations are particularly suitable for use with large core biopsy procedures using such devices as ABBI (United States Surgical, Norwalk, CT) or SiteSelect (Imagyn Medical Technologies, Newport Beach, CA), which may have a coring diameter of 1 to 2.5 cm. Particularly for the ABBI device, a large core of tissue is removed from the skin into the biopsy site. These configurations are also suitable for use in an open biopsy procedure. The devices of Figures 3H-3J are designed to fill the entire biopsy cavity and track, yet adequately mark the actual biopsy site of interest. In such cases it may be desirable to offset the marker from a center of the marking device. Body 336 is preferably trimmable to length, such as by using a scalpel to trim to a length indicated by reference numeral 348 or 350, for example. This allows tracks of varying depths to be adequately filled as required by the depth of the lesion targeted for biopsy. These devices may be deployed through the distal end of a large core biopsy device, or may be inserted after removal of the biopsy device. Coiled markers 334, 338, and 340 are preferably made from radiopaque and/or echogenic wire and partially extend from the distal end of body 336. In one variation, the distal ends 335 of the coiled wire are sharp to penetrate tissue, while their proximal ends 337 are blunt and may include balls 339 as described with respect to Figures 3F and 3G. Although depicted as extending out of the body, the marker (in this variation, the coil) may be designed not to extend out of the body. Sharpened end 335 is screwed into the tissue at the distal end of the biopsy core until the distal end of body 336 abuts the distal side of the cavity. A delivery device may be used to place and/or screw in the marking device, either through a large core biopsy device or after its removal. Body 336 is preferably resorbable, resilient, and hemostatic to aid in stopping the bleeding following a biopsy. As body 336 is resorbed, the proximal portions of marker coils 334, 338, and 340 remain to mark the region of interest within the biopsy cavity. The marker coils may have features to distinguish the proximal portion within or about the body 336 from the distal portion extending from the distal end of the body 336. One such feature is shown in Figure 3H and comprises a transition in coil diameter of the marker coil 334. Other such features may include a color change visible only on direct visualization, as would be available during

open surgical lumpectomy. Alternatively or additionally, there may be differences in echogenicity, radiopacity, coil pitch or any other feature to mark the transition. As another alternative, the transition may not necessarily be marked at all, with the physician knowledgeable that, for example, the portion extending from the body is 2.5 turns of coil, and the portion within the body is 5 turns, or that the transition point is halfway between the proximal and distal end of the coil marker, or the like.

Figure 3K illustrates a cavity marking device comprising three bioresorbable portions 342, 344, and 346 having various resorption rates. This configuration is particularly suitable for open surgical biopsies and lumpectomies. Preferably, portion 342 is filled with air, either air alone, or air within a porous resorbable material such as collagen. The air aids in ultrasonic detection. Preferably, portion 344 is a shell that maintains its integrity for about 2 weeks to about 2 months to temporarily prevent portion 342 from becoming hydrated. Portion 346 surrounds at least part of portion 344, and may comprise a material such as collagen, cellulose, or gelatin that can be trimmed to fit a biopsy or lumpectomy cavity and that can become hydrated when exposed to bodily fluids. This technique of providing materials within materials of various absorption rates may be used to advantage for controlled release of chemotherapeutic, antibiotic, or other agents. For example, portion 342 may contain a therapeutic agent, temporarily surrounded by "shell" layer portion 344, which may comprise gelatin, PEG, or PGA, for example. Surrounding portion 344 may be another portion (not shown) containing a therapeutic agent kept temporarily contained by another "shell" layer (not shown). This layering of drug layers and shell layers can continue, with an outer layer 346 preferably, but not necessarily, trimmable and readily hydratable.

Also, turning back to the marking device 100 in Figure 1A or the marking device 100 of Figure 1B, the markers 150 or 154 may be substituted with one or more suture or wire markers 158, preferably extending through the center and pointing radially away from the center. This configuration allows marking of the cavity perimeter and establishing of the directionality of the cavity itself.

Any of the previously-described additional features of the inventive device, such as presence of pain-killing or hemostatic drugs, the capacity for the marker to emit therapeutic radiation for the treatment of various cancers, the various materials that may make up the

marker and body, and their size, shape, orientation, and geometry, may be incorporated into the device described above in conjunction with Figures 3A-3K.

Turning now to Figures 4A-4C, a method of delivering the inventive device of Figure 1A is shown. Figure 4A details the marking device 402 just prior to delivery into a tissue cavity 404 of human or other mammalian tissue, preferably breast tissue 406. As can be seen, the step illustrated in Figure 4A shows a suitable tubular percutaneous access device 400, such as a catheter or delivery tube, with a distal end 408 disposed in the interior of cavity 404. As previously described, the marking device 402 may be delivered percutaneously through the same access device 400 used to perform the biopsy in which tissue was removed from cavity 404. Although this is not necessary, it is less traumatic to the patient and allows more precise placement of the marking device 402 before fluid begins to fill the cavity 400.

Figure 4B shows marking device 402 being pushed out of the distal end 408 of access device 400 by a pusher 412 and resiliently expanding to substantially fill the tissue cavity 404.

Finally, in Figure 4C, access device 400 is withdrawn from the breast tissue, leaving marking device 402 deployed to substantially fill the entire cavity 404 with radiopaque or echogenic marker 410 suspended in the geometric center of the marking device 402 and the cavity 404. As mentioned above, the marking device 402 may be sized to be larger than the cavity 404 thus providing a significant resistance against the walls of the cavity 404.

Figures 4D-4F show a method of delivering the marking device 402 into a tissue cavity 404 by a plunger 414 that is capable of both advancing the marking device 402 and delivering a biocompatible fluid 416. The "biocompatible fluid" is a liquid, solution, or suspension that may contain inorganic or organic material. The fluid 416 is preferably a saline solution, but may be water or contain adjuvants such as medications to prevent infection, reduce pain, or the like. Alternatively or additionally, the fluid may be used to mark the sentinel lymph node. Obviously, the fluid 416 is intended to be a type that does no harm to the body.

Figure 4D details the marking device 402 prior to delivery into the tissue cavity 404. In Figure 4E, a plunger 414 pushes the marking device 402 out of the access device 400. Upon exiting the access device 400 the marking device 402 begins resiliently expanding to substantially fill the cavity 404.

Figure 4F shows the plunger 414 delivering the biocompatible fluid 416 into the cavity 404. The plunger 414 may be equipped with a Luer or other type fitting to attach a fluid reservoir or syringe (not shown). The fluid 416 aids the marking device 402 in expanding to substantially fill the cavity 404. In this example, the biocompatible fluid 416 is delivered subsequent to the placement of the marking device 402 in the cavity 404. The marking device 402 may also be soaked with fluid 416 prior to placement in the cavity 404. Furthermore, the fluid 416 may be delivered prior to delivery of the marking device 402.

Figures 4G-4I show another method of delivering the marking device 402 into the tissue cavity 404 by using the biocompatible fluid 416 as the force to deliver the marking device 402 into the tissue cavity 404.

Figure 4G details the marking device 402 prior to delivery into the tissue cavity 404. Figure 4H illustrates flow of the biocompatible fluid 416 in the access device 400, the fluid 416 flow then pushes the marking device 402 out of the access device 400.

Figure 4I shows the delivery device 400 continuing to deliver the biocompatible fluid 416 into the cavity 404. The fluid 416 aids the marking device 402 in expanding to substantially fill the cavity 404. In this example, the biocompatible fluid 416 is delivered after the placement of the marking device 402 in the cavity 404 although the invention is not limited to the continued delivery of the fluid 416.

Figures 4J-4L show the method of delivering the body 418 of the cavity marking device directly into the cavity 404 prior to the placement of the marker 410 in the device 402.

Figure 4J shows the deposition of the body material 418 into the cavity 404. In this case the body material 418 may be a gel type material as described above. Figure 4K details the filling of the cavity 404 with the body material 418. At this point, the delivery device (not shown in Figure 4K) may be withdrawn. Figure 4L details the placement of the marker 410 into the body material 418.

Figures 4M-4N show the insertion of a detectable thread-like marker device as it is inserted into a cavity. Figure 4M illustrates an access device 400 depositing a detectable material 420 a cavity 404 within tissue 406. The detectable material 420 is deposited in a thread-like configuration. Figure 4N illustrates the cavity 404 being substantially filled by the detectable thread-like marker. It is intended that a hydraulic source, a pump, a syringe, or a tube-plunger device will be used to deposit the marker 420 into the cavity 404.

Figure 4O illustrates a marker having a detectable outer shell 208, such as the marker illustrated in figure 1Q above, that was previously inserted into a cavity 404. Figure 4P illustrates the detectable outer shell 208 remaining adhered to the margin of the cavity 404 after the bioabsorbable body is absorbed into the body. Accordingly, as the shell 208 remains, it marks the perimeter or margin of the cavity, which is now closed.

Figures 5A-5E show yet another version of the invention in which a marker, preferably consisting of a radiopaque or echogenic wire, is deployed alone into a tissue cavity without the use of any body. In this device, the marker can be made of a shape memory material, such as a nickel-titanium alloy, which, when deployed into the biopsy cavity, assumes a predetermined configuration to substantially fill the cavity, mark the cavity location and margin, and indicate the orientation of the marker inside the cavity. The open design of these deployable markers allows tissue in-growth, that further stabilizes the markers. Furthermore, the periphery of the cavity is marked with a relatively small amount of implanted material.

In Figure 5A, marker 500 is a three-dimensional sphere consisting of two rings 502 and 504 pivotally connected at ends 506 and 508 so to assume a spherical shape. Such a marker can be made of a shape memory metal so that when it is placed in a deployment tube 510 shown in Figure 5B, marker 500 assumes a collapsed profile suitable for deployment through tube 510 by pusher 512. Upon exiting into the tissue cavity (not shown), marker 500 assumes the spherical shape of Figure 5A to fill the cavity. The marker 500 may also be shaped into any similar shape such as an ellipsoidal shape.

Turning now to Figure 5C, a marker 520 in the form of a wire cylinder is shown. Again, this device is structurally configured to assume the depicted cylindrical configuration when deployed in the tissue cavity, but may be (as described above) "collapsed" into a deployment tube for percutaneous delivery. This device is especially suitable for marking the distal and proximal ends of the tissue cavity due to its asymmetrical shape.

Figure 5D shows a shape memory marker 530 in the form of a helical coil deployed into tissue cavity 532. Again, as seen in Figure 5E, such a marker 530 may be deployed through delivery tube 510 by pusher 512 in a substantially elongated, straightened form, only to substantially assume the shape of the cavity 532 as shown in Figure 5D. Any

suitable delivery device or pusher 512 capable of deploying marker 530 into cavity 532 is within the scope of this invention.

Each of the markers shown in Figures 5A-5E is preferably a shape memory material coated or supplemented with a radiopacity-enhancing material, such as gold, platinum, or any other radiopaque material herein discussed. The markers may singly, or in combination with being radiopaque, be echogenic or be made echogenic by any of the materials or methods herein described.

Each of the markers shown in Figures 5A-5E is preferably self-centering. It is within the scope of the invention to add one or more materials such as a biocompatible liquid, gel, powder, or the like into the cavity before, during, or after delivery of those markers; the material may provide treatments such as hemostasis, antibiotic properties, or pain relief. In addition, a marker of any of the type shown in Figures 2A-2H may be inserted into the optional material to mark the center or provide patient information as described with respect to Figure 2F.

Figures 6A-6D show a method of delivering the marking device 602 into a tissue cavity 604 that allows the marking device 602 to radially expand to substantially fill the cavity 604 without the need for simultaneous pushing of the marking device 602 into the cavity 604. While the marking device 602 depicted in Figures 6A-6D is depicted as a bioabsorbable surgical material with a marker placed at the geometric center of the device, the method is not limited to such devices. Any of the marker devices described herein may be used with this method.

Figure 6A details insertion of a sheath 600 into communication with tissue cavity 604. Preferably, the sheath 600 is placed through the same access pathway (not shown) used by the biopsy device (not shown). The sheath 600 is placed soon after the cavity 604 is formed.

Figure 6B illustrates insertion of a cartridge or applicator 606 through the sheath 600 and into the cavity 604. The cartridge 606 may contain a marking device 602 and a disengaging arm (not shown.) Preferably, the cartridge 606 is advanced into the cavity 604 until the marking device 602 is located within the cavity 604.

Figure 6C illustrates the withdrawal of the cartridge 606 from the cavity 604 and the partial expansion of the cavity marking device 602. As shown in the figure, the disengaging arm 608 within the cartridge 606 permits withdrawal of the cartridge 606

independently of the marking device 602. Thus, the marking device 602 remains within the cavity 604. The use of the disengaging arm 608 permits the placement of the marking device 602 while allowing for a significant frictional fit between the marking device 602 and the cartridge 606. This frictional fit minimizes the possibility of accidental deployment of the marking device 602.

Figure 6D illustrates the withdrawal of the cartridge 606 and the disengaging arm 608 from the cavity 604 leaving the marking device 602 to radially expand into the cavity 604. Although it is not shown, after the marking device 602 is placed within the cavity 604, fluid (not shown) may be delivered to the cavity 604 to assist the expansion of the marking device 602. Ultimately, the sheath 600 and cartridge 606 are withdrawn from the cavity 604 and further withdrawn from the body.

Figures 7A-7K show devices for delivering a marking device into a tissue cavity which allow the marking device to radially expand to substantially fill the cavity without the need for simultaneous pushing of the marking device into the cavity.

Figure 7A illustrates a variation of a disengagement arm 700 having distal 704 and proximal 702 ends. The disengagement arm 700 of this figure has first and second slots 706 and 708 that allow for a cartridge 710 and sheath 716 to have fixable positions along the disengagement arm 700. Although it is not shown, the disengagement arm 700 may be configured to have a lumen (not shown) to provide delivery of fluid to the cavity to assist with the expansion of the marking device (not shown).

Figure 7B illustrates a variation of a cartridge 710 having a lumen 712 for placement of a marking device (not shown). The cartridge 710 has an offset member 714 visible in Figure 7C. In this embodiment, the offset member 714 engages with the first slot 706 of the disengagement arm 700 to define a fixable position of the cartridge 710 along the disengagement arm 700. Figure 7D illustrates a sheath 716 having an offset member 718, as shown in Figure 7E, which engages with the second slot 708 of the disengagement arm 700 to define a fixable position of the sheath 716 along the disengagement arm 700. The cartridge 710 may be rotated about the disengagement arm 700 so that the offset member 714 is removed from the slot 706 allowing the cartridge 710 to be moved to the proximal end of the disengagement arm 700.

Figure 7F shows another variation of a disengagement arm 720 having distal 724 and proximal 722 ends. The disengagement arm 720 of this variation has a stop 726 that

allow for a cartridge 730 and sheath 736 to have fixable positions along the disengagement arm 720. Figure 7G shows a variation of a cartridge 730 having a lumen 732 for placement of a marking device (not shown). The cartridge 730 has a flange 734, as shown in Figure 7H, which rests against the stop 726 of the disengagement arm 720 to provide the cartridge 730 with a fixable position along the disengagement arm 720. The cartridge 730 may be rotated about the disengagement arm 720 so that an opening 738 in the flange 734 allows the cartridge 730 to be moved to the proximal end of the disengagement arm 722. On the cartridge 730 of Figure 7G, a sheath may have a fixable position along the cartridge 730 as the sheath is placed against a proximal end 742 of the cartridge 730. Figure 7I shows a variation of the sheath 736 for use with the disengagement arm 720 and cartridge 730 of Figures 7F and 7G. Although it is not shown, the disengagement arm 720 may be configured to have a lumen (not shown) to provide delivery of fluid to the cavity to assist with the expansion of the marking device (not shown).

Figure 7J illustrates the variations of the cartridge devices against a proximal end of the disengagement arms 720 and 700. Figure 7K illustrates the variations of the cartridge devices in a fixable position along the disengagement arms 720 and 700. In these positions, the end portions 748 and 740 of the cartridges 720 and 700 extend beyond the distal ends 724 and 704 of the disengagement arms.

Figures 8A-8I illustrate a delivery device 800 and a method for using it to deliver a marking device 860 to a tissue cavity 874 accessed and/or made by the probe 882 of a medical instrument 880. The probe 882 is preferably between 1 and 25 mm in its largest cross sectional dimension (diameter, if circular), and most preferably between 2 and 5 mm. Although the marking device 860 is shown as the type shown in Figure 1K, it is not limited to such, and may be of any type disclosed in this application or any other type.

As seen in Figure 8A, the delivery device 800 includes an outer sheath 810 having a proximal entryway 812 for the probe 882 (shown in Figure 8B). The outer sheath 810 further includes an outer sheath hub 814 and an optional side port 816. The outer sheath 810 may be circular or noncircular in cross section regardless of whether the probe 882 has a circular or noncircular cross section. For example, if the outer sheath 810 is flexible and circular in cross section, but the probe 882 is shaped like a "figure 8", the outer sheath 810 may conform to follow the contours of the probe when the outer sheath is placed over the probe. For example, for a probe having such a figure 8 configuration with its largest cross

sectional dimension about 4.6 mm and its smallest about 3 mm; the outer sheath may have a circular cross section with an inner diameter of about 4 mm. The delivery device 800 further includes an applicator 820, which is made up of an inner sheath 830 and a plunger 840. The inner sheath 830 may further comprise an inner sheath hub 832, a safety lock 834 with a safety tab 835, a stop 836, and a distal portion 838 that is distal of the stop 836. A marking device 860 may be preloaded within the distal portion 838 of the inner sheath 830. For the example above of a 4-mm inner diameter outer sheath, the inner sheath will easily accommodate a marking device having a compressed diameter up to about 3.3 mm. The inner sheath hub 832 is preferably immovable on the inner sheath 830, providing both a grip for pushing the plunger 840 and a support for the safety lock 834. Furthermore, the inner sheath hub 832 may also function as a stop, thereby eliminating the need for separate stop 836. The distal portion 838 of the inner sheath 830 is sized to fit through either the entryway 812 or the side port 816 of the outer sheath 810 up to the inner sheath stop 836. The delivery device 800 preferably includes a guide 850 having a clamp 852 for attachment to a first point that is fixed with respect to a desired marking site within the patient. This first fixed point could be, for example, on the patient herself, on a stereotactic table, or on an attachment on a stereotactic table, such as a rail, a fixed portion of a driver attached to the stereotactic table, or the like. The guide 850 has a channel 854 through which the outer sheath 810 may slide. The guide 850 also has a locking mechanism 856 that can engage the outer sheath hub 814. The inner and outer sheaths are preferably made of an extruded polyether block amide of the type sold under the name PEBAX (Atachem North America, Inc., Philadelphia, PA), a fluoropolymer such as TEFLON (E.I., duPont de Nemours and Co., Wilmington, DE), or polyethylene, and may be radiopaque or echogenic. The hubs 814 and 832 and guide 850 are preferably made of polycarbonate or polypropylene.

As shown in Figure 8B, to use the delivery device 800, the outer sheath 810 is placed over a probe 882 of a medical instrument 880, such as a biopsy probe.

As shown in Figure 8C, a guide 850 preferably is attached, using a clamp 852, to a first point 858 that is fixed with respect to the patient 870, such as a fixed point on the medical instrument 880, a rail of a stereotactic table 890 (as shown), or the patient herself. The probe 882 with the outer sheath 810 is introduced through the channel 854 of the guide 850, through the skin 872 of the patient 870, and into the site where the marker is to be

deployed; this step may comprise taking a tissue sample, thus creating a cavity 874 in the tissue.

As shown in Figure 8D, while the probe 882 and outer sheath 810 are held stationary with respect to the patient 870, the guide 850 is moved from the first fixed point 858, then slid along the outer sheath 810 toward the outer sheath hub 814 to a second fixed point 859 along the rail of the stereotactic table 890. (Alternatively, the second fixed point 859 may be a point on the medical instrument 880 or the patient 870 or other convenient place to keep the outer sheath 810 stationary with respect to the patient 870 during delivery of the marking device.) The guide 850 is connected to the outer sheath hub 814, such as with a friction or snap fit of the locking mechanism 856.

As shown in Figure 8E, the medical instrument 880 is then at least partly retracted from both the patient 870 and the stationary outer sheath 810, leaving the outer sheath 810 in communication with the biopsy cavity 874. If a side port 816 is used, as shown, the probe 882 may be retracted just far enough to allow access to the cavity through the side port 816; the distal end of the probe 882, which is typically sharp, may remain protected by the proximal end of the outer sheath 810, and is not required to be retracted past the outer sheath entryway 812. However, if a side port 816 is not provided on the outer sheath 810 or is otherwise not used, the probe 882 must be fully retracted to clear the entryway 812. Furthermore, for side port access, the outer sheath 810 may be rotated within the guide 850 to ensure that side port 816 is oriented to be accessible to the operator.

As shown in Figure 8F, an applicator 820 comprising an inner sheath 830 and a plunger 840 preferably is inserted into a side port 816 of the outer sheath 810 until the stop 836 is reached and the distal end 831 of the inner sheath 830 protrudes through the distal end 818 of the outer sheath 810. The inner sheath 830 is preferably flexible to bend to access the side port 816. Alternatively, it may be preshaped in a bend or curve to access the side port 816. Furthermore, plunger 840 is flexible to access side port 816; it, too, may have a preshaped curve. Alternatively, the probe 882 may be retracted clear of the proximal entryway 812, and the applicator 820 may be inserted through the proximal entryway 812.

Figures 8G-8I illustrate deploying the marking device 860. As shown by the arrow in Fig. 8G, a safety lock 834 is unlocked by depressing a safety tab 835 on the applicator 820 to release the plunger 840. The plunger 840 is pushed into the inner sheath 830, as

shown by the arrow in Fig. 8H, to deploy the preloaded marking device 860 into the tissue cavity 874, as shown in Fig. 8I. Although not shown, a Luer or other type fitting may be provided on the delivery device for fluid infusion. The delivery device 800 is removed from the patient 870.

The delivery device of Figures 8A-8I may be used to deliver a marking device to a surgically-created cavity by introducing the distal end of the outer sheath through the surgical incision and into the cavity.

Figures 9A-9F illustrate a delivery device 900 and a method for using it to deliver a marking device 960 to a tissue cavity 974 laterally through a side window 986 of a cannula 982 of a medical instrument 980. (See Figure 9D.) Although the marking device 960 is shown as the type shown in Figure 1K, it is not limited to such, and may be of any type disclosed in this application or any other type known in the art. It is preferably implantable without needing to be removed. The medical instrument 980 may be a biopsy device as described above, or may be any other medical instrument having a cannula 982 with an entryway 988 through which the delivery device 900 can enter, a stop 984 that can limit travel of the delivery device 900, and a side window 986 proximate the distal end 985 through which the marking device 960 can be deployed. The probe 982 is preferably between 1 and 25 mm in its largest cross sectional thickness (diameter, if circular), and most preferably has an inner diameter of 2.5 to 4 mm. The stop 984 may completely or only partially block the distal end 985 of the cannula 982 or may be located elsewhere to limit travel of the delivery device 900.

As shown in Figures 9A-9B and by way of example, the delivery device 900 preferably includes a shaft 920, which has a flexible shaft portion 930, a proximal handle portion 932, a rotational position indicator 934, and a cutout 936 in the proximal handle portion 932 for mating with a feature 989 of the medical instrument 980 (shown in Figure. 9C). This feature 989 may be the tip of a slidable rod that aids in ejecting a tissue sample from the medical instrument 980, which in this case is shown as a biopsy instrument. As shown in Figures 9D-9F, the flexible shaft portion 930 is flexible enough in bending to allow it to be introduced through the entryway 988 of the cannula 982 of the medical instrument 980, yet stiff enough in compression to allow it to be pushed through the cannula 982. Distal of the flexible shaft portion 930 is a distal shaft portion 938, comprising an ejector 940 having a seat 942 on which the preloaded marking device 960

(shown in Figure 9D) rests prior to delivery and from which the marking device 960 is ejected laterally through the side window 986 of the cannula 982 (shown in Figure 9F). The ejector 940 further comprises one or more living hinges 944. The entire shaft 920 except for the proximal handle portion 932 is sized to fit through the cannula 982 of the medical instrument 980 (shown in Figure 9E), and is preferably molded or machined of only one material, such as polypropylene, nylon, or acetal (Delrin®). The flexible shaft portion 930 is more flexible than the proximal portion of the ejector 940. This flexibility may be brought about by varying thickness (using a flexible shaft portion 930 that is thinner, or smaller diameter, if the shaft is round, than the thickness or diameter of the proximal portion of the ejector 940). Alternatively, this greater flexibility may be obtained by varying the shape of the cross section. As another alternative, this greater flexibility may be obtained by using a more flexible material for the flexible shaft portion 930 than for the proximal portion of the ejector 940. As yet another alternative, the section desired to be less flexible may be laminated with a stiff tubing.

As shown in Figure 9D, to use the delivery device 900, the cannula 982 of the medical instrument 980 is introduced through the skin 972 of the patient 970 and into the site where the marking device 960 is to be deployed. As described before, this step may comprise taking a tissue sample, thus creating a cavity 974 in the tissue. In that case, the side window 986 and lumen of the cannula 982 are then cleared of tissue debris, such as by applying a vacuum; additionally, the cannula may be flushed with saline, which is then aspirated. The shaft 920 is preloaded with a marking device 960, which sits in the seat 942. The marking device 960 is preferably held in place by a retainer 910, which may comprise a tube (as shown), a block, a clip, or the like. In the case where the retainer 910 is a tube, it is preferably made of polyethylene teraphthalate (PET). Furthermore, the seat 942 itself may be designed to provide substantial friction between it and the marking device 960 to help retain the marking device 960 within the seat 942. In fact, the retainer 910, while preferable, is not essential. The friction between the marking device 960 and seat 942 may be increased by adding texture to the surface of the seat 942 and/or by furnishing a seat of a size and shape to provide an interference fit between the marking device 960 and the seat 942.

As shown in Figure 9E, the distal end of the shaft 920 is placed through the cannula entryway 988 and aligned so that the marking device 960 is in line with the side window

986. The rotational position indicator 934 in proximal handle portion 932 aids in determining the orientation of the marking device 960. In the case where the retainer 910 is a tube, block, clip, or the like, the retainer 910 may be transient as shown, sliding toward the proximal end of the shaft 920 as the delivery device 900 enters the cannula 982. The marking device 960 remains captured between the seat 942 and the cannula 982 as the shaft 920 with marking device 960 is slid through the cannula 982. This differs from some of the prior art clipping devices that are carried on a wire that must be cut when the clip reaches its intended location.

As shown in Figure 9F, using the proximal handle portion 932, the shaft 920 is advanced so that the distal end of the shaft 920 contacts the cannula stop 984. Advancement of the shaft 920 continues until the ejector 940 ejects the marking device 960 from the seat 942, through the cannula side window 986, and into the tissue cavity 974. As shown here, the ejection step may occur by buckling the shaft 920 in the region of the ejector 940, pushing the seat 942 toward the cannula side window 986. This may be facilitated by using one or more living hinges 944. A cutout 936 in the proximal handle portion 932 may be mated with a mating feature 989 in the medical instrument 980 to indicate that the shaft 920 is in the correct position such that the ejector 940 has ejected the marking device 960. Preferably, the ejector 940 remains completely within the cannula 982 without any portion of it passing through the side window 986. This helps to ensure that the marking device 960 is delivered directly out of the side window 986 without pushing it to some unknown location further away. The retainer 910 may comprise a tube having a slit 912 or other means of expanding its proximal end to fit over the proximal handle portion 932. The retainer 910 preferably remains captured on the shaft 920 between the proximal handle portion 932 and the cannula entryway 988. Although not shown, after the marking device 960 has been ejected through the side window 986, the cannula 982 preferably is rotated about 180° so that the side window 986 is away from the deployed marking device 960. The medical instrument 980 and delivery device 900 are then retracted from the patient 980. Preferably, the ejector 940 is designed to substantially cover the window 986 of the medical instrument 980 to prevent drag on and/or injury to tissue or the marking device on the way out.

Figures 10A-10H illustrate an alternative delivery device 1000 and method for using it to deliver a marking device 1060 to a tissue cavity 1074 laterally through the side

window 1086 of a cannula 1082 of a medical instrument 1080. The delivery device 1000 is similar to that of delivery device 900 in that its main features are (1) an ejector seat for holding and ejecting a marking device laterally through a side window while remaining within the cannula and (2) a flexible shaft for pushing the ejector seat and marking device through the cannula. The medical instrument 1080 may be a biopsy device as described above, or may be any device having a cannula 1082 with an entryway 1088 through which the delivery device 1000 can enter, and a side window 1086 proximate the distal end 1085 through which the marking device 1060 can be deployed. The cannula 1082, and therefore the portion of the delivery device sliding through cannula 1082, is preferably between 1 and 25 mm in its largest cross sectional thickness (diameter, if circular), and most preferably has an inner diameter of 1.5 to 4.5 mm. In a preferred embodiment, cannula 1082 has an inner diameter of about 2.7 mm, allowing delivery of a marking device 1060 having a compressed diameter of about 2.5 mm. Although the marking device 1060 is shown as the type shown in Figure 1L, it is not limited to such, and may be of any type disclosed in this application or any other type known in the art. The marking device 1060 is preferably one that can be simply released into the marking site without requiring clipping or piercing tissue.

As shown in Figure 10A, the delivery device 1000 includes an applicator 1020, which has a sheath 1030 and a plunger 1040. A portion of sheath 1030 and a portion of plunger 1040 together form a flexible shaft portion 1022, which can bend to fit through entryway 1088 and is rigid enough to push the ejector seat with its marking device through the cannula 1082. The sheath 1030 further comprises a proximal handle portion 1032 and a collapsible sleeve 1031 at or near its distal end. As shown in Fig. 10B, sleeve 1031 forms an ejector seat 1033, preferably U-shaped, in its collapsed condition on which the preloaded marking device 1060 rests prior to delivery and from which the marking device 1060 is ejected through the side window 1086 of the cannula 1082 (shown in Fig. 10C). The sleeve 1031 is preferably made of a high yield strength plastic such as PET, polyimide, polycarbonate, or acrylic, and is preferably of a size and shape that the material does not have to yield when expanding to eject the marking device 1060. The sleeve 1031 and distal portion of the sheath 1030 are sized to fit through the cannula 1082 of the medical instrument 1080 (shown in Figure 10C). The sheath 1030 further comprises a clip 1035 that is preferably immovable on the sheath 1030, and includes one or more features 1036,

such as a notch, indentation, recess or hole, to mate with a feature 1089 on the medical instrument 1080 (shown in Fig. 10C). The sheath 1030 is preferably made of PEBAX, a fluoropolymer such as TEFLON, or polyethylene, and is preferably radiopaque and/or echogenic. The clip 1035 is preferably made of polycarbonate or polypropylene. The plunger 1040 further comprises a proximal handle portion 1042 and a piston 1045 and is capable of expanding the sleeve 1031 by filling it with an expander 1044, which may be a fluid, such as saline or air, or preferably a solid, such as the distal portion of the piston 1045 as shown. In the case where the expander 1044 is a fluid, the sleeve 1031 may be sealed to form a balloon that keeps the fluid within the delivery device. Alternatively, the sleeve 1031 may have one or more openings (not shown) to allow the fluid to not only expand the sleeve 1031 but to be delivered to the body; this is useful for delivering fluids having hemostatic, pain-reducing, antibiotic, sentinel node-detecting, and/or body-expanding properties; the body expanding properties may work by hydrating or by chemically reacting with the body material. To inject the fluid through the plunger 1040, whether the sleeve 1031 is open or closed, the plunger 1040 may further include a Luer or other type fitting for connection to a fluid reservoir or syringe (not shown). Additionally or alternatively, fluids may be infused through a vacuum system on the medical instrument. In the case where the expander 1044 is a solid, the sleeve 1031 may be open or closed.

As shown in Figure 10C, to use the delivery device 1000, the cannula 1082 of the medical instrument 1080 is introduced into the site where the marking device 1060 is to be deployed; as described before, this step may comprise taking a tissue sample, thus creating a cavity 1074 in the tissue. The side window 1086 and lumen of the cannula 1082 are preferably cleared of tissue debris, such as by applying a vacuum; additionally, the cannula may be flushed with saline, which is then aspirated. The applicator 1020 is preloaded with a marking device 1060, which sits in the ejector seat 1033 formed in the collapsed sleeve 1031. It is held in place by a retainer 1010, which may be a tube (as shown), a block, a clip, or the like, of a size that will not pass through the cannula 1082.

As shown in Figure 10D, the distal end of the applicator 1020 is placed through the cannula entryway 1088 and aligned so that the marking device 1060 is in line with the side window 1086. This alignment can be achieved by ensuring that the side window 1086 is in its "12 o'clock" rotational position, as shown, and orienting the marking device 1060 so that it is facing the same direction as the side window 1086 and so that the clip 1035 with

its mating feature(s) 1036 will match up with the feature 1089 on the medical instrument 1080. Because the retainer 1010 cannot pass through the cannula 1082, it is a transient retainer and does not remain in place to hold the marking device 1060 in seat 1033; as the delivery device 1000 enters the cannula 1082, the retainer 1010 is slid off the marking device 1060 and remains outside the cannula 1082. The marking device 1060 remains captured between the seat 1033 and the cannula 1082 as the applicator 1020 with its marking device 1060 is slid through the cannula 1082.

As shown in Figures 10E-10H, the applicator 1020 is advanced until the clip 1035 on the sheath 1030 abuts the proximal end of the retainer 1010, thus capturing the retainer 1010 between the clip 1035 and the cannula entryway 1088. The clip 1035 is then clipped onto the medical instrument 1080 by mating the clip and medical instrument features, 1036 and 1089. The plunger 1040 is then pushed until the expander 1044 expands the sleeve 1031, ejecting the marking device 1060 from the seat 1033, through the cannula side window 1086, and into the tissue cavity 1074. Preferably, all parts of the applicator 1020 that enter the cannula 1082 remain completely within the cannula 1082 without any portion passing through the side window 1086. This helps to ensure that the marking device 1060 is delivered directly out of the side window 1086 without pushing it to some unknown location further away. As shown in Fig. 10G-10H, after the marking device 1060 has been ejected through the side window 1086, the cannula 1082 is preferably rotated about 180° so that the side window 1086 is away from the deployed marking device 1060. This guarantees that only a smooth, non-cutting side of the cannula faces the marking device 1060 during withdrawal of the medical instrument 1080 to avoid dislodging the marking device 1060. Furthermore, an advantage of this system is that once the sleeve is expanded it substantially covers the side window thus protecting the tissue. In fact, prior art through-cannula clip delivery devices typically require extra steps of withdrawing the clip applier and reinserting an inner cannula to protect the tissue from the sharp window and to avoid dislodging the clip. The medical instrument 1080 and delivery device 1000 are then retracted from the patient 1070.

Figures 11A-11E illustrate an alternative delivery device 1100 and method for using it to deliver a marking device 1160 to a tissue cavity 1174 laterally through the side window 1186 of a cannula 1182 of a medical instrument 1180. The medical instrument 1180 is preferably a biopsy device as described above, or may be any device having a

cannula 1182 with an entryway 1188 through which the delivery device 1100 can enter, and a side window 1186 proximate the distal end 1185 through which the marking device 1160 can be deployed. Although the marking device 1160 is preferably the type shown in Figure 1L, it is not limited to such, and may be of any type disclosed in this application or any other known in the art. Marking device 1160 is preferably implantable and can be left in the body indefinitely.

As shown in Figure 11A, the delivery device 1100 includes an applicator 1120, which has a sheath 1130 and a plunger 1140. A portion of the sheath 1130 and a portion of the plunger 1140 together form a form a flexible shaft portion 1122, which can bend to fit through entryway 1188 and is rigid enough to push the ejector seat with its marking device through the cannula 1182. The sheath 1130 further comprises a proximal handle portion 1132 and a collapsible sleeve 1131 that forms an ejector seat 1133 in its collapsed condition (similar to seat 1033 shown in Fig. 10B) on which the preloaded marking device 1160 (shown in Figure 11C) rests prior to delivery and from which the marking device 1160 is ejected through the side window 1186 of the cannula 1182. The sleeve 1131 is preferably made of a high yield strength plastic such as PET, polyimide, polycarbonate, or acrylic, and is preferably of a size and shape that the material does not have to yield when expanding to eject the marking device 1160. The sheath 1130 further comprises a clip 1135 that is immovable thereon, having a clip feature 1136. The plunger 1140 further comprises a proximal handle portion 1142 and a piston 1145 and is capable of expanding the sleeve 1131 by filling it with an expander 1144, which may be a fluid, such as saline or air, or preferably a solid, such as the distal end of piston 1145 as shown. In the case where the expander 1144 is a fluid, the sleeve 1131 is sealed to form a balloon. Alternatively, the sleeve 1131 may have one or more openings (not shown) to allow the fluid to not only expand the sleeve 1131 but to be delivered to the body; this is useful for delivering fluids having hemostatic, pain-reducing, antibiotic, sentinel node-detecting, and/or body-expanding properties; the body expanding properties may work by hydrating or by chemically reacting with the body material. In the case where the expander 1144 is a solid, the sleeve 1131 may be open- or closed-ended. A separate fitting may be provided on the sheath 1130 for drug or saline infusion through the sheath 1130. The distal end of the applicator 1020 is sized to fit through the cannula 1182 of the medical instrument 1180 (shown in Figure 11C). The delivery device 1100 further includes a retainer 1110 having a

key on its distal end for locking into a keyway 1183 in the cannula 1182 (shown in Fig. 11B). The retainer 1110 further includes a hub 1114 at or near its proximal end with a feature 1115 for connecting to the clip feature 1136 on the sheath clip 1135.

As shown in Figure 11C, to use the delivery device 1100, the cannula 1182 of the medical instrument 1180 is introduced into the site where the marking device 1160 is to be deployed; as described before, this step may comprise taking a tissue sample, thus creating a cavity 1174 in the tissue. The side window 1186 and lumen of the cannula 1182 are preferably cleared of tissue debris, such as by applying a vacuum; additionally, the cannula may be flushed with saline, which is then aspirated. The applicator 1120 is preloaded with a marking device 1160, which sits in the seat 1133 (see seat 1033 in Fig. 10B) formed in the collapsed sleeve 1131. It is held in place by the retainer 1110, which may be a tube (as shown), a block, a clip, or the like. As will be seen later, it is not necessary that the side window 1186 of the cannula 1182 be in its "12 o'clock" position to align the marking device 1160 with the side window 1186. The keyway 1183 rotates with the cannula 1182, and therefore is in line with the side window 1186.

As shown in Figure 11D, the distal end of the applicator 1120 and retainer 1110 are placed through the cannula entryway 1188 and aligned so that the retainer key 1112 enters keyway 1183 of the cannula 1182. As the delivery device 1100 enters the cannula 1182, the retainer 1110 is slid off the marking device 1160. The applicator 1020 is pushed forward, aligning the feature 1136 in the sheath clip 1135 with the feature 1115 in the retainer hub 1114 and connecting them together, thus capturing the retainer 1110 between the cannula entryway 1188 and the sheath clip 1135. By locking the sheath clip 1135 to the retainer hub 1114, and because the retainer 1110 is locked into the keyway 1183 and is therefore rotationally fixed with respect to the cannula 1182, the marking device 1160 will always face the direction that the side window 1186 is facing. Therefore, the marking device 1160 may be delivered when the medical instrument 1180 has its cannula 1182 and side window 1186 in any clock position, and is not limited to delivering in only the 12 o'clock position. The marking device 1160 remains captured between the seat 1133 and the cannula 1182 as the applicator 1120 with its marking device 1160 is slid through the cannula 1182.

As shown in Figure 11E, the safety lock 1134 on the proximal handle portion 1132 is then unlocked, and the plunger 1140 is pushed until the expander 1144 expands the

sleeve 1131, ejecting the marking device 1160 from the seat 1133, through the cannula side window 1186, and into the tissue cavity 1174. Preferably, all parts of the applicator 1120 that enter the cannula 1182 remain completely within the cannula 1182 without any portion passing through the side window 1186. This helps to ensure that the marking device 1160 is delivered directly out of the side window 1186 without pushing it to some unknown location further away. After the marking device 1160 has been ejected through the side window 1186, the cannula 1182 is rotated about 180° so that the side window 1186 is away from the deployed marking device 1160. As with delivery device 1000, an advantage of delivery device 1100 is that once the sleeve is expanded it substantially covers the side window 1186 thus protecting the tissue. The medical instrument 1180 and delivery device 1100 are then retracted from the patient 1170.

As can be seen from the embodiments of Figures 9A-9F, 10A-10G, and 11A-11E, delivery of a marking device into a cavity through a window provides several advantages. As examples, the track created is only as large as the cannula used to create the cavity, the number of steps in the procedure is reduced because the site is positively located by the cannula itself and does not have to be relocated, and the marking device will be delivered to the correct location.

From the foregoing, it is understood that the invention provides an improved subcutaneous cavity marking device and method. While the above descriptions have described the invention for use in the marking of biopsy cavities, the invention is not limited to such. One such application is evident as the invention may further be used as a lumpectomy site marker. In this use, the cavity marking device yields an improved benefit by marking the perimeter of the lumpectomy cavity. Other such applications of the invention include delivering a marker to a naturally occurring body cavity and delivering a marker to an area of tissue that does not have a cavity. Furthermore, although some of the embodiments described herein were described with respect to a percutaneous procedure, they may be used in an open surgical procedure as well; in that case, the marking device may be delivered by hand without the use of a delivery system, and the marking device may not require compression for delivery through a small opening. Also, the marking system may be provided as a kit, wherein the marking device is preloaded in the delivery device; alternatively, the marking device may be provided separately for loading into the delivery device by the operator, with or without the aid of a loading tool, which also may

be provided in the kit. The kit may be provided with variously sized and/or variously shaped marking devices, allowing the operator to choose the particular device most suited for the cavity to be marked. Having more than one marking device available in the kit also allows the operator to mark more than one location, if needed. Furthermore, for cavities that are significantly larger than the available marking devices, more than one marking device may be placed in a single cavity. Also, it may be desirable to place a second marking device in a biopsy track that leads to a marked cavity.

Sentinel Node Marking:

Furthermore, as will be described with respect to Figures 12A-12C and 13A-13B, the present invention provides an alternative composition and method to remotely detect sentinel lymph nodes to determine whether cancerous cells have spread thereto. This method includes the deposition, preferably by one of the delivery devices described herein or by injection via a thin needle applicator, of a remotely detectable contrast agent that migrates to the SN. Upon accumulating in the SN, the remotely detectable contrast agent allows a physician to pinpoint the location of the SN to target the SN for removal using minimally invasive techniques. The composition is preferably capable of migrating from breast tissue to a lymph node in a predetermined amount of time, preferably, less than 3 hours, and more preferably within 5 to 20 minutes. To migrate within this timeframe, the contrast agent preferably comprises particles between 0.05 microns and 5 microns in diameter. The composition and method eliminates the need for potentially toxic radioactive tracer material. In addition, the lack of toxicity of such agents obviates the need to remove the lesion and/or the SN on the same day. The contrast agent is preferably either permanently implantable or short-lived, never requiring removal.

These agents may be any biologically compatible agents capable of remote detection. Examples of such remote detection include, but are not limited to, magnetism such as a magnetometer, Hall effect sensor, or magnetic resonance imaging (MRI); ultrasound; X ray, fluoroscopy, or CT; thermal means; high intensity ultraviolet techniques; fluorescent dye techniques; etc.; singly or in combination.

One example of such a contrast agent is an echogenic microsphere capable of reflecting ultrasonic energy. These microspheres, preferably averaging typically between 0.2 microns and 5 microns in diameter, and preferably less than 2 microns in diameter, may

be mixed with a biologically compatible carrier fluid and injected into the body in the vicinity of the lesion, where they will accumulate in the SN. The echogenic microspheres may comprise hollow bubbles filled with air, carbon dioxide, nitrogen, or fluorinated gas. For example, these microbubbles may comprise microencapsulated perfluorocarbon. The echogenic contrast agent may, but does not necessarily, contain microparticles of silicon or a silicon compound, such as silicone or SiO_2, preferably in a dilute suspension. Such silica microspheres are available from Bangs Laboratories, Inc. Fishers, IN. Upon an exposure to ultrasonic energy, the spheres reflect the energy creating an ultrasonic reflection. The ultrasonic-reflection resulting from a large number of the microspheres that have accumulated in the SN permits detection of the particular node by a conventional ultrasonic probe. Another example of an agent is a biologically compatible magnetically detectable body such as a magnetic microsphere. Such a magnetically detectable body can be the echogenic microsphere described above that is either fabricated from or coated with a magnetic material; alternatively, it may be a solid or other type of magnetic body capable of being incorporated into a carrier fluid and deposited around the lesion or its cavity as described herein. These bodies should be capable of migration to and accumulation in the SN so that, in a similar fashion to the echogenic microspheres, the cumulative magnetic field presented by these magnetic bodies allows one to remotely and noninvasively determine the location of the SN.

As an alternative or addition to being echogenic, the contrast agent may have sufficient radiopacity to be detectable using fluoroscopy, mammography, or other X ray imaging.

Figures 12A-12C show a method for locating the sentinel lymph node in a mammalian body to determine if cancerous cells have spread thereto. The method includes (1) depositing a remotely detectable fluid in or around a lesion for migration to and accumulation in the associated sentinel node and (2) remotely detecting the location of that node with a minimum of trauma and toxicity to the patient. The composition used for locating the sentinel node is preferably a fluid composition consisting of a carrier fluid and some type of non-radioactive contrast agent as described above. Alternatively, the contrast agent may also be a fluid and therefore not require a separate carrier fluid to migrate to the node. This composition is capable of (1) deposition in or around a lesion and migration to and accumulation in the associated sentinel node, and (2) remote detection a noninvasive

technique. The composition may additionally be capable of being directly visualized such as by adding blue dye to the noninvasively-detectable contrast agent to confirm that the appropriate lymph node was removed. Carbon may be, but is not necessarily, added to the contrast agent for histological confirmation.

Figure 12A depicts the first steps of a method for locating a sentinel node 1200 comprising injecting a noninvasively detectable, non-radioactive, migratory contrast agent 1210 into the region of a cavity or lesion 1220, then waiting sufficient time for the contrast agent to migrate through the lymph ducts 1230 to at least one lymph node 1200 in the axillary region 1250. In general, the smaller the particle size of the contrast agent, the faster it will migrate; also, generally less viscous compositions will migrate faster. Furthermore, the closer in the size the particles are to each other, the narrower the window of time will be for most of the particles to reach the sentinel node. The particles may be filtered or otherwise selected to be very close in size; alternatively, they may vary widely; as another alternative, they may have a bimodal size distribution with the smaller size for early sentinel node detection and the larger size for accumulation throughout the lymph nodes, as will be described below. The contrast agent may be injected directly into a biopsy or lumpectomy cavity; or it may be injected intradermally or periareolarly (around the area of the areola 1240), before, after, or without creation of a cavity. While waiting for the contrast agent to migrate, massage and/or compression may be administered to the patient to speed migration of the contrast. Also, a biopsy or lumpectomy may be performed during the waiting period, if not already done (not shown). This latter order of steps may be preferred by some who believe that creating the cavity may disturb the lymph ducts 1230, slowing down or preventing migration of the contrast agent to the sentinel node.

As shown in Figure 12B, the contrast agent 1210 is noninvasively detected in at least one lymph node 1200. Examples of non-invasive detection methods include, but are not limited to using ultrasound, fluoroscopy, MRI, a Hall effect sensor or magnetometer, or other imaging means. In the embodiment depicted in Figure 12B, the contrast agent 1210 is echogenic, and an ultrasound probe 1260 is used to scan the axilla 1250 while watching the ultrasound monitor 1270. Preferably, only one lymph node is identified as containing contrast agent and, therefore, is the "sentinel node"; however, the contrast agent may accumulate in two or three lymph nodes almost simultaneously, with up to three being

considered "sentinel nodes", as shown. Particularly for contrast agents having a low viscosity and a uniformly small size, such as an average of less than 0.05 microns and an upper limit of 0.1 microns, lymphatic system will quickly take up the contrast agent. The contrast agent will then quickly migrate to the sentinel node, then to the next node and so on. In that case, the physician must be careful to not wait too long between injection and detection.

As shown in Figure 12C, lymph tissue containing the contrast agent 1200 is then either sampled, using fine needle aspiration (FNA) or core biopsy, or completely removed, percutaneously, endoscopically, laparoscopically, or using conventional surgery. A percutaneous tissue removal device 1280 may be used, such as those described in U.S. Patent Nos. 5,913,857, 5,810,806, and 6,036,698, and U.S. Patent Application Serial No. 09/145,487 to Vivant Medical, Inc. The tissue sampling or removal is preferably done using ultrasound, especially in the case where ultrasound is used to detect the contrast agent. The ultrasound probe 1260 held over the sentinel node 1200 that was detected in the axilla 1250 while the marked tissue is sampled. Alternatively or additionally, the tissue sampling or removal may be done using fluoroscopy, especially in the case where the contrast agent is radiographic. As another alternative, the tissue sampling or removal may be done using MRI. Many of the prior-art radioactive tracer methods required separate procedures for detecting the sentinel node under the skin, marking the location on the skin with a dot, alternating between a gamma probe and an ultrasound probe to mark the SN with a wire, then surgically removing the SN and wire. However, in the present invention, it is desirable to use the same imaging modality to detect the sentinel node and to sample or remove it. Following the sentinel lymph node sampling or removal, the patient may be noninvasively checked to see whether all the contrast was removed. However, it is preferable that the contrast be completely implantable, not requiring removal. Furthermore, many of the commercially-available echogenic contrast agents suitable for this method are short-lived, and therefore do not require removal.

The removed tissue is evaluated histologically for cancer. If cancer is found in the sentinel lymph node, the migrating and accumulating properties of the contrast agent can be used to determine where additional lymph nodes are that should be removed. That is, the contrast agent that was used to detect the SN can be one that accumulates quickly in the first node ("sentinel node") for identification within preferably 5 to 20 minutes. The agent

will continue to migrate through the lymphatic system, but preferably more slowly, with a portion of the contrast agent accumulating in each lymph node for detecting during a window of approximately 1 day to 1 month following injection. This facilitates detection of additional lymph nodes that the physician may want to remove in the case where cancer is detected in the sentinel node. Removing such lymph nodes may be therapeutic by decreasing the tumor burden, thus increasing the efficacy of subsequent chemotherapy. The lymph nodes preferably are removed percutaneously using image guidance of the same modality used to detect them.

Figures 13A-13B show a method for marking a biopsy or lumpectomy cavity and locating the sentinel lymph node that had served the tissue removed from the cavity to determine if cancerous cells have spread thereto. The composition for locating the sentinel lymph node is preferably a fluid composition consisting of a carrier fluid and some type of contrast agent as described above; alternatively, the contrast agent may itself be a fluid and therefore not need a separate carrier fluid. This composition is capable of (1) deposition in or around a lesion and migration to and accumulation in the associated sentinel node, and (2) detection, preferably by noninvasive means, and/or by direct visualization. Also disclosed is a method for marking a cavity and detecting the location of a sentinel node by (1) depositing a marking device with a detectable composition in the cavity for migration to and accumulation in the associated sentinel node and (2) detecting the location of that node with a minimum of trauma and toxicity to the patient.

Figure 13A depicts the first steps of a method for marking a biopsy or lumpectomy cavity 1315 in the breast 1313 and locating a sentinel node 1300 in the axilla 1350, comprising inserting a subcutaneous marking device 1312 according to the present invention and using a delivery device 1305 according to the present invention. A contrast agent 1310 is included in the marking device 1312, either as the body of the marking device (as shown), which may degrade, allowing detectable microparticles to migrate to the lymph nodes. Alternatively, the contrast agent 1310 as a separate composition that is added to the marking device, before, during, or after its insertion into the cavity (e.g., see Figures 4D-4I, 10A-10H, and 11A-11E). Following marking device/contrast agent insertion, while waiting for the contrast agent to migrate to a lymph node, massage and/or compression may be administered to the patient to speed migration of the contrast.

In a similar manner as depicted in Figure 12B, the contrast agent is noninvasively detected in at least one lymph node. Examples of such non-invasive methods includes, but are not limited to, ultrasound, fluoroscopy, MRI, or a Hall effect sensor or magnetometer, or other imaging. The imaging used to detect the contrast agent may be, but is not necessarily, the same as that used to detect the cavity marking device.

As shown in Figure 13B, lymph tissue containing the contrast agent is then either sampled, using fine needle aspiration (FNA) (shown here) or core biopsy, or completely removed, endoscopically, laparoscopically, or using conventional surgery. As shown in this example, marking device 1312 has expanded to fill cavity 1315. Some of the contrast agent 1310 has migrated away from the marking device 1312 and has accumulated in the sentinel node 1300, where an ultrasound probe 1360 is used to guide a needle 1390 for fine needle aspiration. As described above, the tissue sampling or removal may be done using ultrasound, fluoroscopy, MRI, or any other suitable imaging technique. Alternatively, the contrast agent may be visible under direct visualization, and the tissue may be surgically removed without any image guidance. As another alternative, the contrast agent may be a radioactive tracer, and a gamma probe and/or lymphoscintigraphy may be used in combination with ultrasound, as described above, to detect and remove the sentinel node. A percutaneous tissue removal device may be used, such as those described in PCT publication WO 99/25248; U.S. Patent Nos. 5,913,857, 5,810,806, and 6,036,698; and U.S. Patent Application Serial No. 09/145,487 to Vivant Medical, Inc.

Once removed, the tissue sample is evaluated for the presence of cancer. If cancer is found in the sentinel lymph node, the contrast agent can again be used to determine where additional lymph nodes are that should be removed. As described above, a contrast agent can be used that will accumulate quickly in the first remaining node ("sentinel node") for identification within preferably 5 to 20 minutes. The agent will continue to migrate through the lymphatic system, but more slowly, with a portion of the contrast agent accumulating in each lymph node for detecting during a window of approximately one day to one month following injection. This provides an easy way to detect the additional lymph nodes that may need to be removed in the case where cancer is detected in the sentinel node. The lymph nodes preferably are removed using image guidance of the same modality used to detect them.

The invention herein has been described by examples and a particularly desired way of practicing the invention has been described. However, the invention as claimed herein is not limited to that specific description in any manner. Furthermore, the features described for one embodiment may be combined with other embodiments herein disclosed.

Equivalence to the description as hereinafter claimed is considered to be within the scope of protection of this patent.

We claim as our invention:

1. A system for tissue modification comprising:
(a) a source for generating a field;
(b) a detectable marker for marking tissue, said marker being detectable by producing a signal upon exposure to the field,
(c) a device for modifying the tissue, and
(d) at least one sensor disposed on the device configured to use the signal for sensing proximity to the marker.

2. The system of claim 1 wherein said source is configured to generate an ultrasound field transmitting a plurality of frequencies and wherein said detectable marker is configured to produce a particular signal upon exposure to a particular frequency.

3. The system of claim 1 wherein said source is configured to generate an alternating current induced magnetic field.

4. The system of claim 1 wherein said detectable marker has a bioabsorbable filler body.

5. The system of claim 1 further comprising a feedback device for relaying proximity information to a user.

6. The system of claim 5 wherein the feedback device is a visual display.

7. The system of claim 6 wherein the visual display is alphanumeric.

8. The system of claim 6 wherein the visual display is graphic.

9. The system of claim 6 wherein the visual display is both alphanumeric and graphic.

10. The system of claim 5 wherein the feedback device is a virtual reality display.

11. The system of claim 5 wherein the feedback device is audio.

12. The system of claim 5 wherein the feedback device is tactile.

13. The system of claim 1 wherein the device is adapted for modifying tissue by cutting.

14. The system of claim 1 wherein the device is adapted for modifying tissue by ablation.

15. The system of claim 1 wherein the device is adapted for modifying tissue by coagulation.

16. The system of claim 1 wherein the device is adapted for modifying tissue by utilizing energy selected from the group comprising mechanical energy, cryoablation energy, radio frequency energy, microwave energy, ultrasonic energy, chemical energy, electrochemical energy, thermal energy, optical energy, or by any combination thereof.

17. The system of claim 1 wherein the device is adapted for removing tissue.

18. The system of claim 1 additionally comprising a tissue removal device.

19. The system of claim 1 wherein the marker is magnetic.

20. The system of claim 1 wherein the marker is radiopaque.

21. The system of claim 1 wherein the marker is bioabsorbable.

22. The system of claim 1 wherein the sensor is a magnetic sensor.

23. The system of claim 22 wherein the sensor is a magnetoresistive sensor.

24. The system of claim 1 wherein the sensor is a Hall effect sensor.

25. The system of claim 1 wherein the sensor is an inductance sensor.

26. The system of claim 1 wherein the marker is echogenic.

27. The system of claim 1 wherein the sensor is an ultrasound sensor.

28. The system of claim 1 wherein the sensor is a pulse-doppler sensor.

29. The system of claim 1 wherein the sensor is a radioactive sensor.

30. The system of claim 1 wherein the sensor is a infrared sensor.

31. The system of claim 1 wherein the sensor is a thermal sensor.

32. The system of claim 1 wherein the sensor is a light sensor.

33. The system of claim 1 further comprising a computer readable medium configured to translate a signal from the sensor to a feedback device.

34. The system of claim 33 wherein the feedback device is a visual display.

35. A tissue modification device comprising at least one sensor capable of detecting a marker disposed in tissue, the sensor in communication with a control system adapted to instantaneously determine a location of the marker in space and a distance of the marker relative to the sensor as tissue is modified using a signal obtained from the marker in response to an applied field.

36. A computer-readable medium containing instructions for controlling a computer system to display (1) information regarding a location of a detectable marker disposed within tissue and (2) information regarding a distance of the marker relative to at least one sensor by:

(a) analyzing at least one signal generated by the sensor containing the location information and the distance information,

(b) converting the signal into a computer readable data, and

(c) transforming the computer readable data into data readable by a feedback device.

37. A method for modifying tissue in a patient comprising the steps of:

generating a field,

placing a detectable marker in the patient to mark tissue for modification, said marker being detectable by producing a signal upon exposure to a field ,inserting a tissue-modifying device having a proximity sensor adapted to sense the marker into the patient,

directing the device to the tissue to be modified using the proximity sensor, and modifying the tissue.

38. The method of claim 37 further comprising the step of removing at least a portion of the tissue from the patient.

39. The method of claim 37 further comprising the step of leaving at least a portion of the tissue in the patient.

40. The method of claim 37 wherein the patient may leave a facility at which the method takes place after completion of the placing step but before commencement of the inserting step.

41. The method of claim 37 further comprising the step of removing the marker from the patient.

42. The method of claim 37 in which the marker is left in the patient.

43. A method for determining a location and a distance of a lesion in tissue relative to a surgical cutting device comprising the steps of:
applying a field to the tissue;
detecting the lesion marked by a detectable marker with the surgical cutting instrument;
approaching the lesion with the surgical cutting instrument; and
removing the lesion from the mass of tissue.

44. A method for determining a location and distance of a lesion in tissue relative to a surgical cutting device comprising the steps of:
applying a field to the tissue;
deploying a detectable marker within tissue to mark a generally volumetric center of the lesion;
detecting the detectable marker with the surgical cutting instrument;
approaching the lesion with the surgical cutting instrument; and
removing the lesion from the mass of tissue.

45. A subcutaneous cavity marking device comprising:

(a) at least one filler body comprising a resilient bioabsorbable material, said filler body having an outside surface; and

(b) at least one detectable marker affixed about said outside surface of said filler body, where said marker has a length of approximately 0.030 inches and an outer dimension from a first side to a second opposite side of approximately 0.095 inches.

46. The cavity marking device of claim 45 wherein said marker has a shape of a band and wherein said outer dimension is an outer diameter.

47. A subcutaneous cavity marking device comprising:

(a) at least one filler body comprising a resilient bioabsorbable material, and

(b) at least one spirally wound detectable thread-like marker within said filler body.

48. The cavity marking device of claim 47 wherein said thread-like marker is helically wound.

49. A method of marking a tissue cavity comprising the steps of:

(a) inserting a detectable bioabsorbable material having a thread-like form into a cavity, and

(b) filling the cavity with the detectable bioabsorbable material until the material occupies a substantial volume of the cavity.

50. A device for marking a biopsy cavity comprising

(a) a detectable bioabsorbable material; and

(b) a delivery means for delivering the bioabsorbable material into the biopsy cavity in a thread-like configuration.

51. A subcutaneous cavity marking device comprising:
(a) at least one filler body comprising a bioabsorbable thread-like material, and
(b) at least one detectable marker deposited on said filler body.

52. The marking device of claim 51 wherein said marker is deposited on said filler body by a process selected from the group of painting, coating, dipping, spraying, and co-extruding.

53. A subcutaneous cavity marking device comprising:
(a) a filler body comprising a bioabsorbable material; and
(b) a detectable shell covering said body.

54. The cavity marking device of claim 53 wherein said shell is porous.

55. The cavity marking device of claim 53 wherein said shell comprises a silicone rubber.

56. The cavity marking device of claim 53 wherein said bioabsorbable material comprises a bioabsorbable liquid.

57. The cavity marking device of claim 53 wherein said shell further comprises an adhesive located on an outer surface of said shell.

58. The cavity marking device of claim 53 wherein said shell is radiopaque.

59. The cavity marking device of claim 53 wherein said shell is echogenic.

60. The cavity marking device of claim 53 wherein said shell is visually detectable.

61. The cavity marking device of claim 53 wherein said shell is magnetically detectable.

62. The cavity marking device of claim 53 wherein said filler body comprises collagen and said shell comprises an adhesive.

63. The cavity marking device of claim 62 wherein said adhesive is radiopaque.

64. The cavity marking device of claim 62 wherein said adhesive is echogenic.

65. The cavity marking device of claim 62 wherein said adhesive is visually detectable.

66. The cavity marking device of claim 62 wherein said adhesive is magnetically detectable.

67. A subcutaneous cavity marking device comprising:
(a) at least one filler body comprising a resilient bioabsorbable material, said filler body having a length of about 0.3 inches to about 0.5 inches and a maximum compressed outer width of about 0.05 inches to about 0.1 inches; and
(b) at least one detectable marker attached to said filler body.

68. The device of claim 67 wherein said length is about 0.5 inches and said maximum compressed outer width is about 0.1 inches.

69. The device of claim 67 wherein said filler body has a compressed form and an uncompressed form and wherein said compressed form has a circular cross section and said uncompressed form has a rectangular cross section.

70. The device of claim 69 wherein said compressed circular cross section has a diameter of approximately 0.1 inches and wherein said uncompressed rectangular cross section has a width of approximately 0.2 inches.

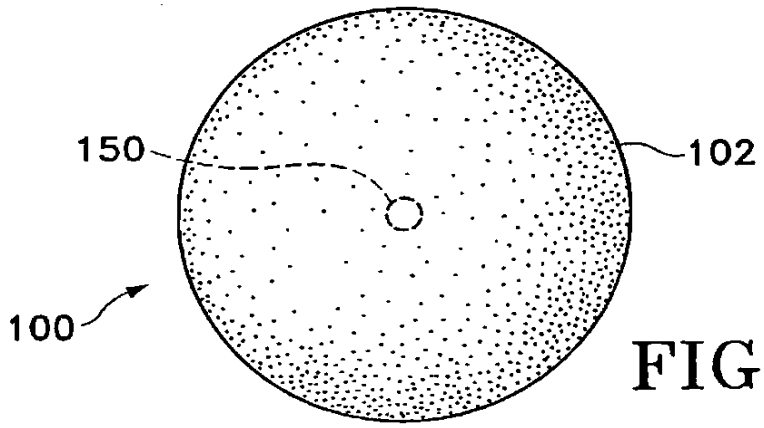


FIG. 1A

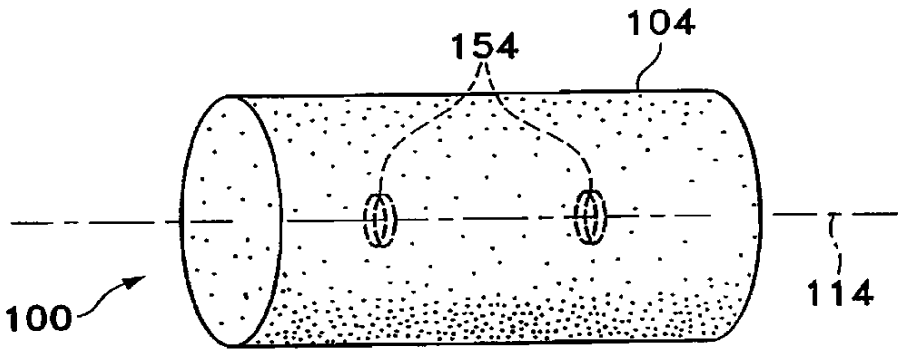


FIG. 1B

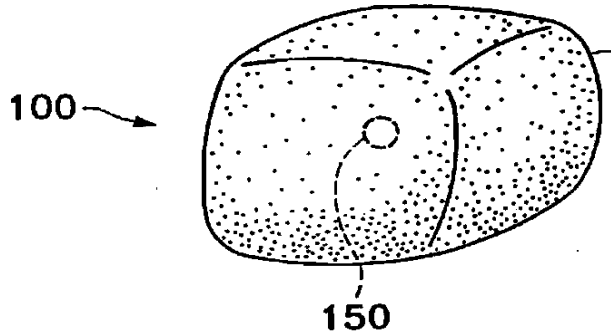


FIG. 1C

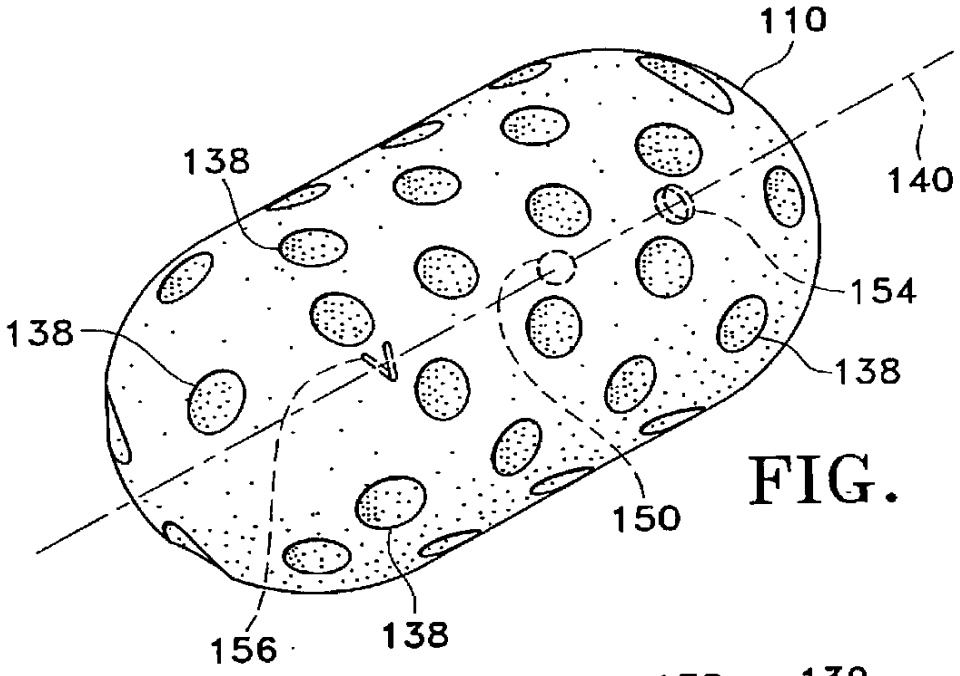


FIG. 1D

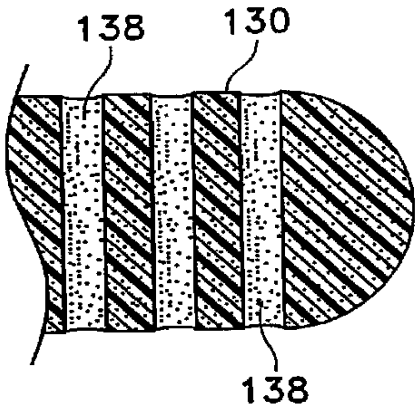


FIG. 1E

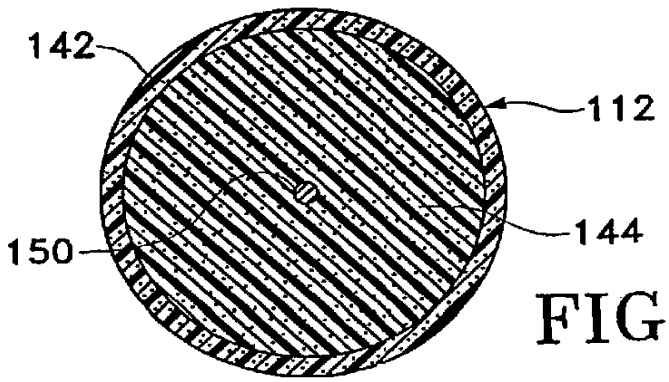


FIG. 1F

FIG. 1G

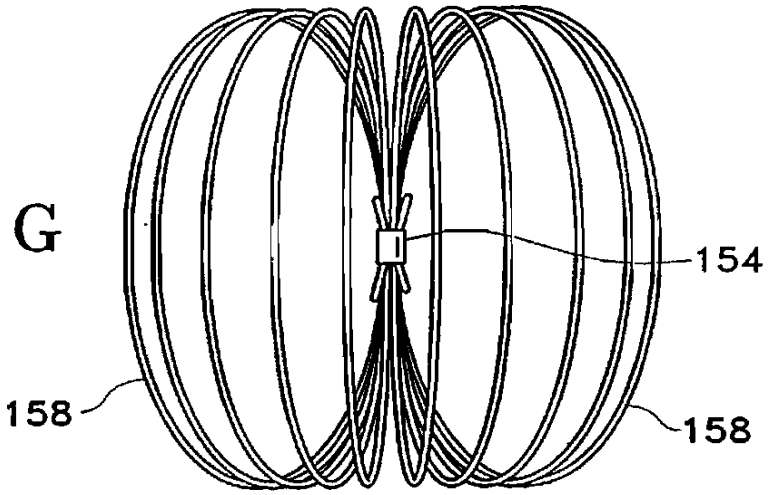


FIG. 1H

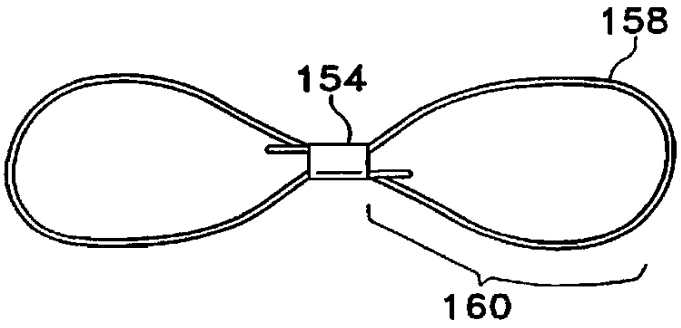
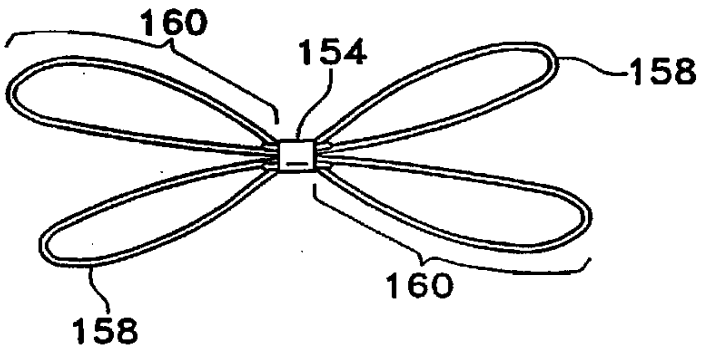


FIG. 1I



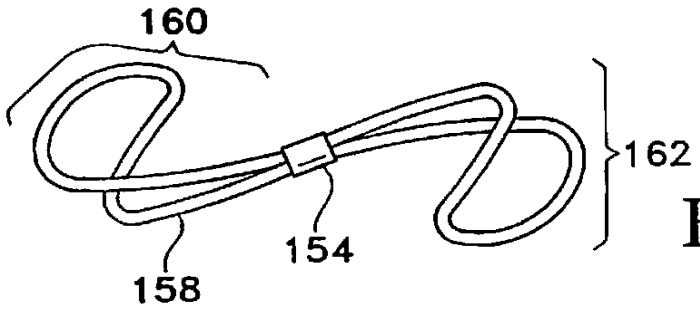


FIG. 1J

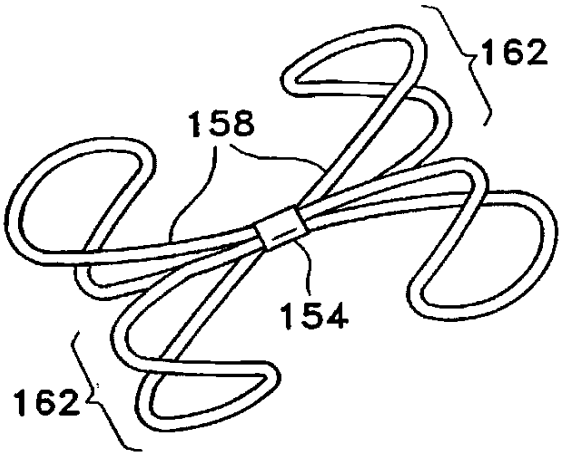


FIG. 1K

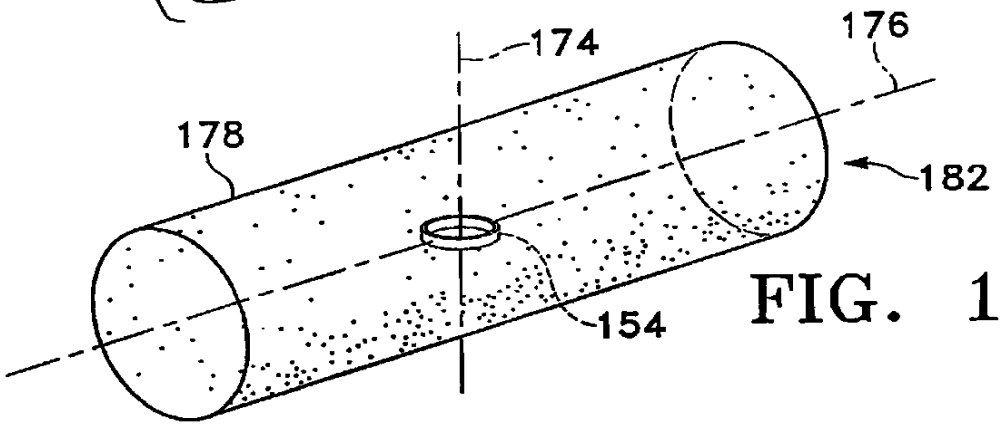


FIG. 1L

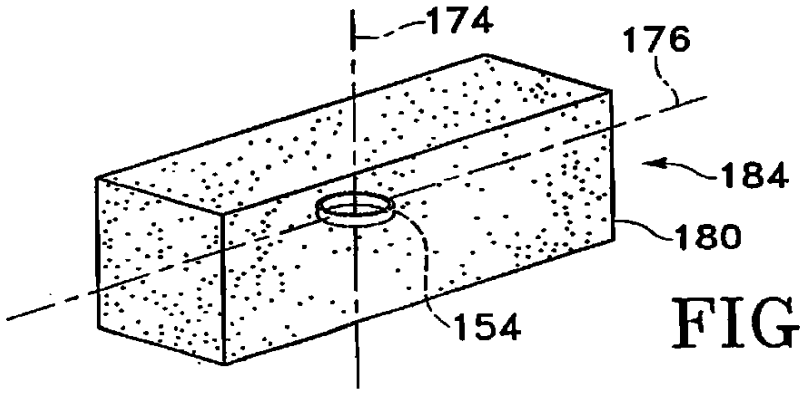


FIG. 1M

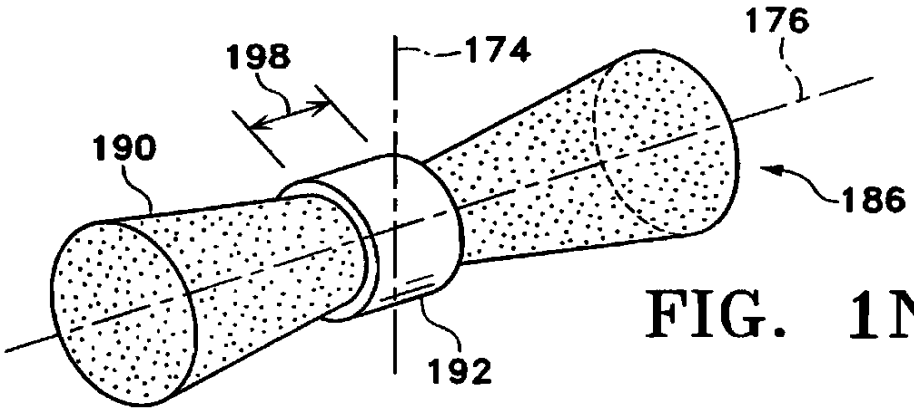


FIG. 1N

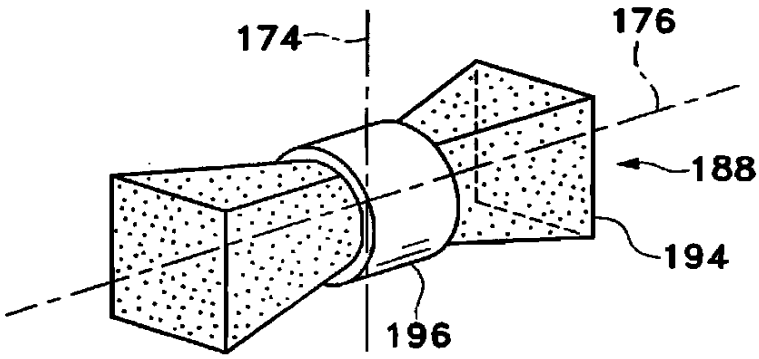


FIG. 1O

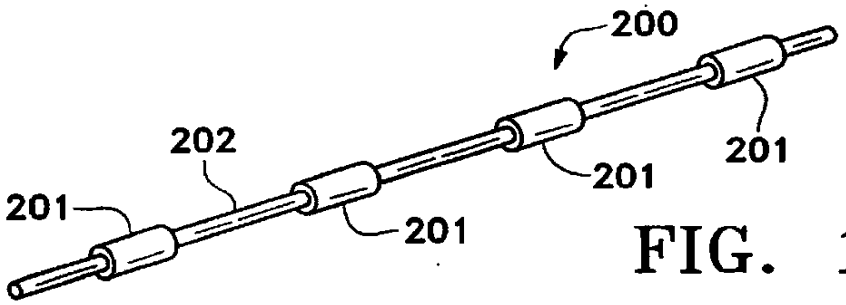


FIG. 1P

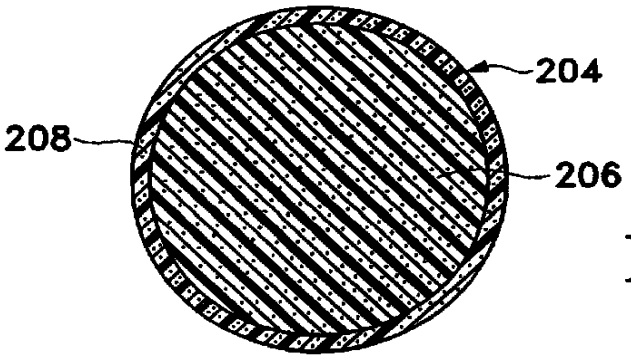


FIG. 1Q

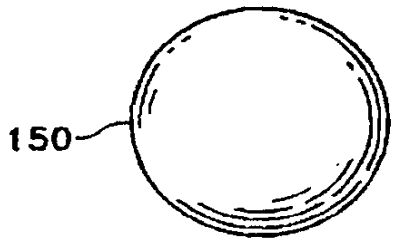


FIG. 2A

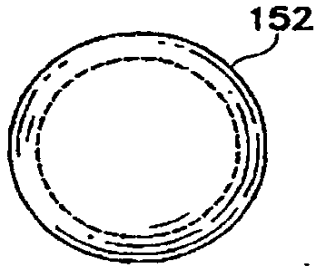


FIG. 2B

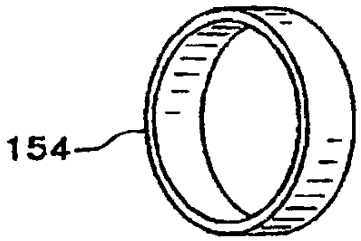


FIG. 2C

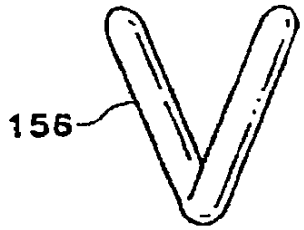


FIG. 2D

FIG. 2E

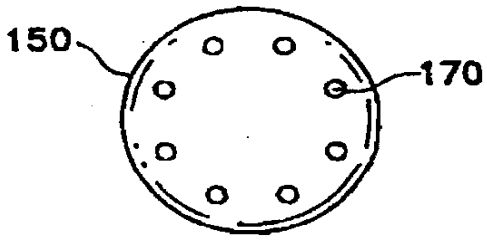


FIG. 2F

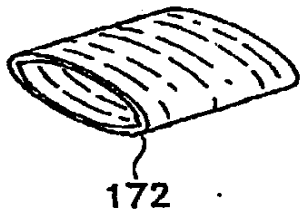


FIG. 2G

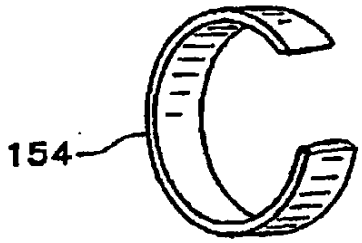


FIG. 2H

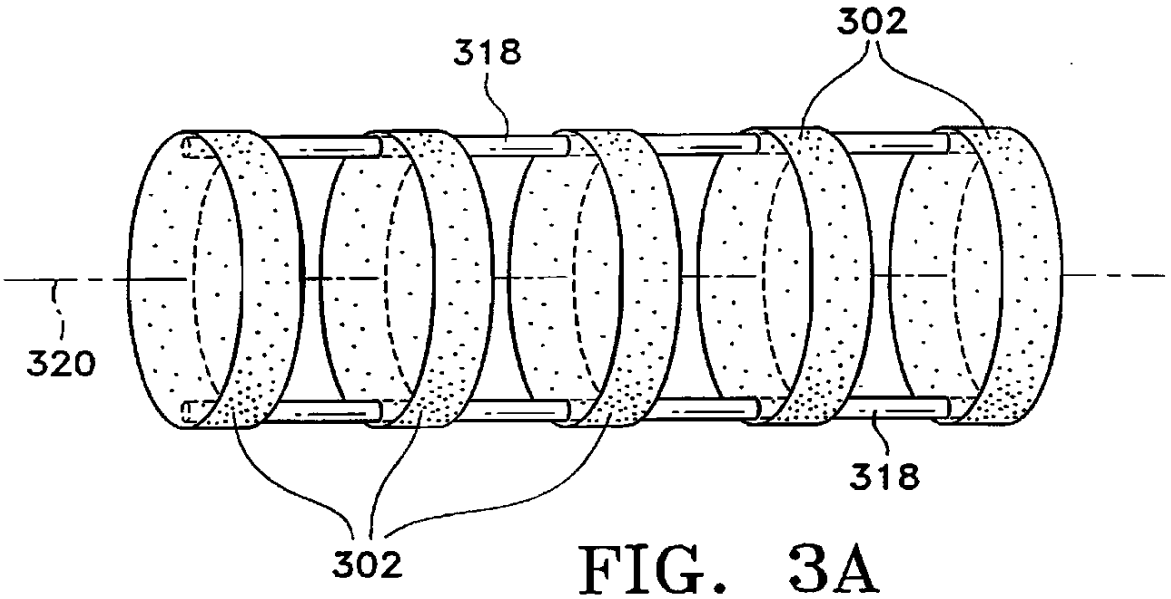


FIG. 3A

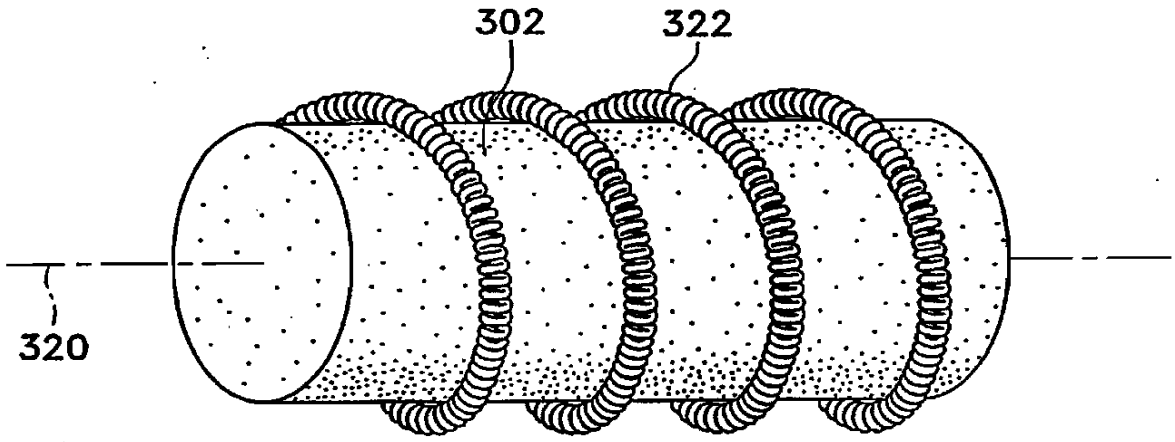


FIG. 3B

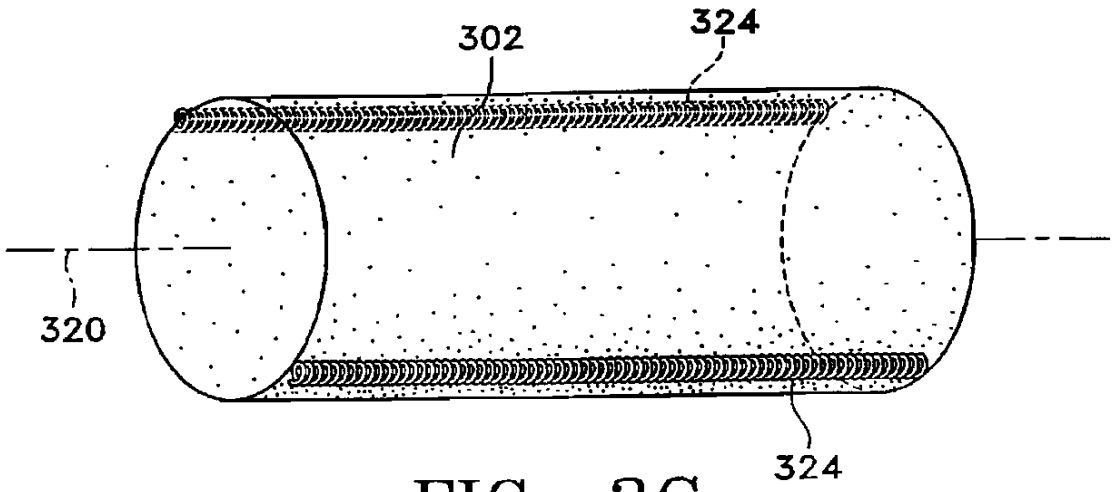


FIG. 3C

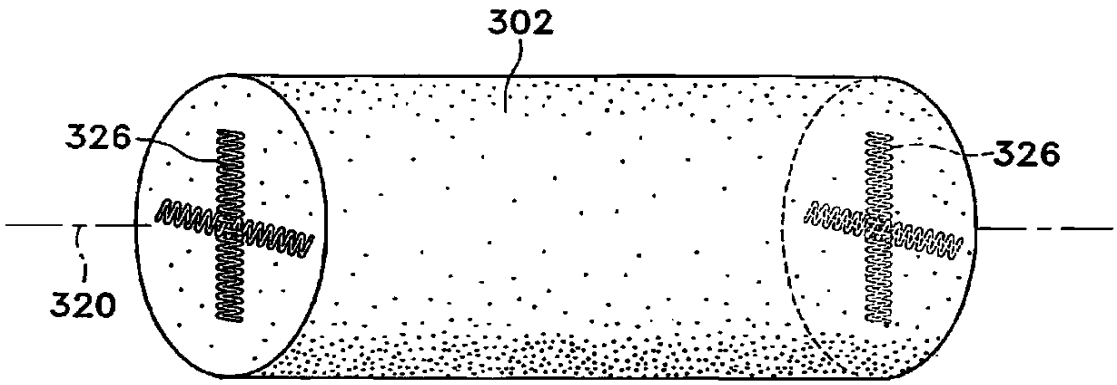


FIG. 3D

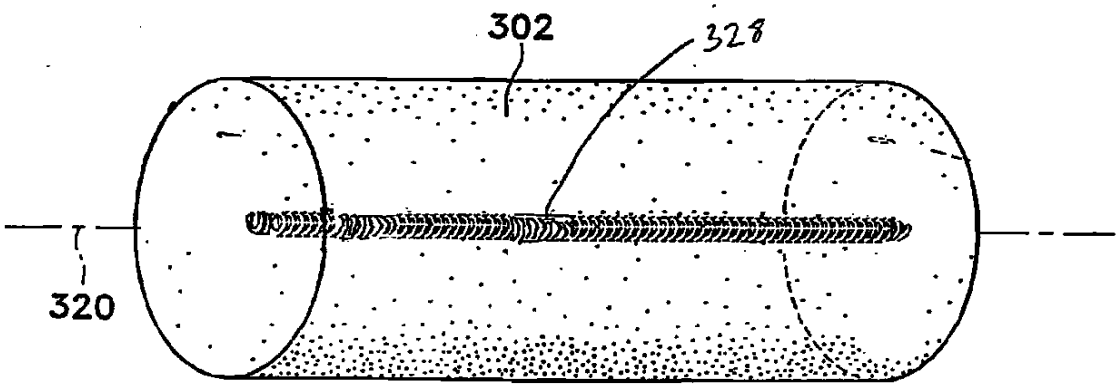


FIG. 3E

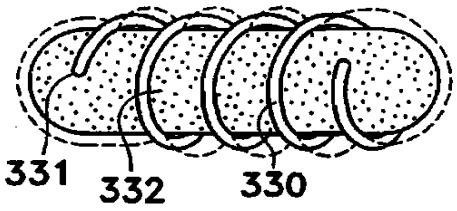


FIG. 3F

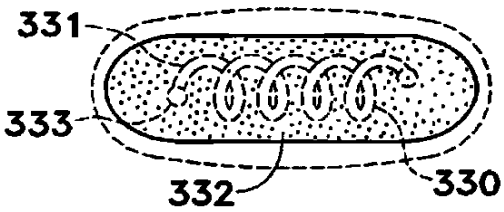


FIG. 3G

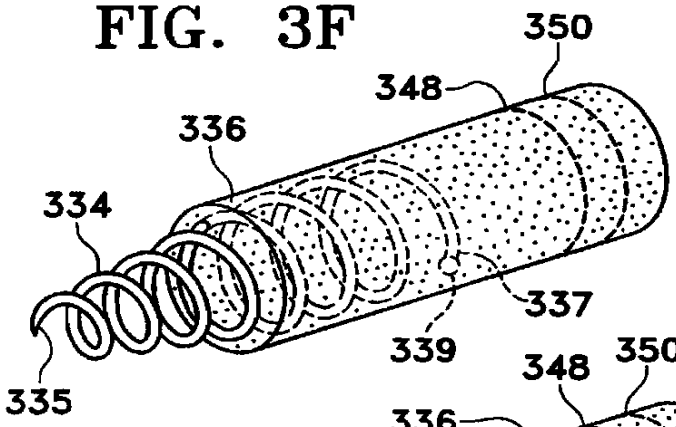


FIG. 3H

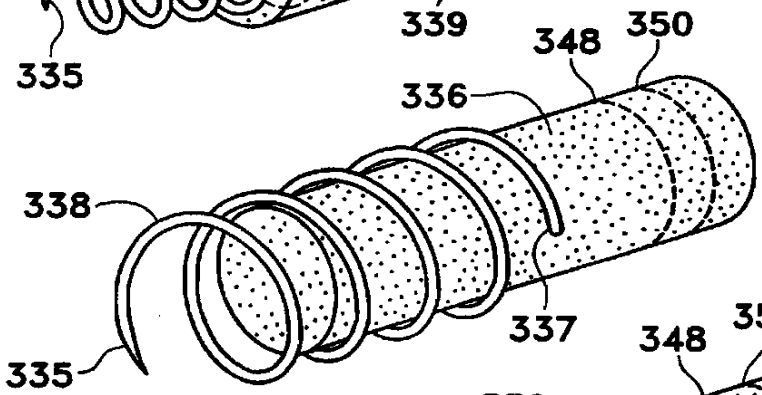


FIG. 3I

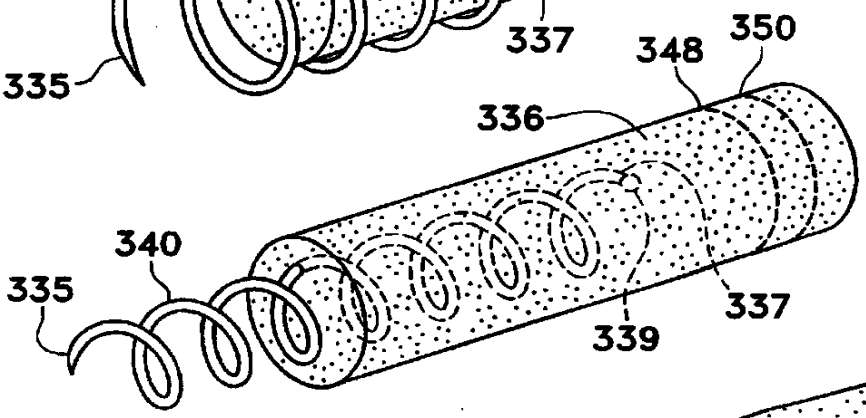


FIG. 3J

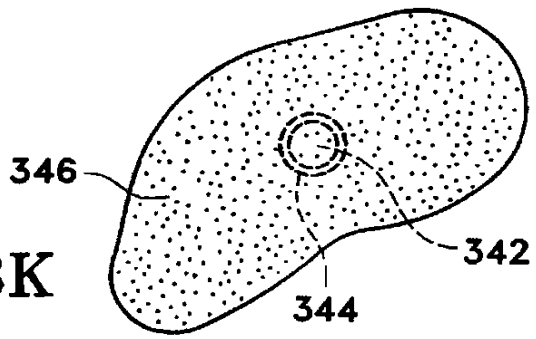


FIG. 3K

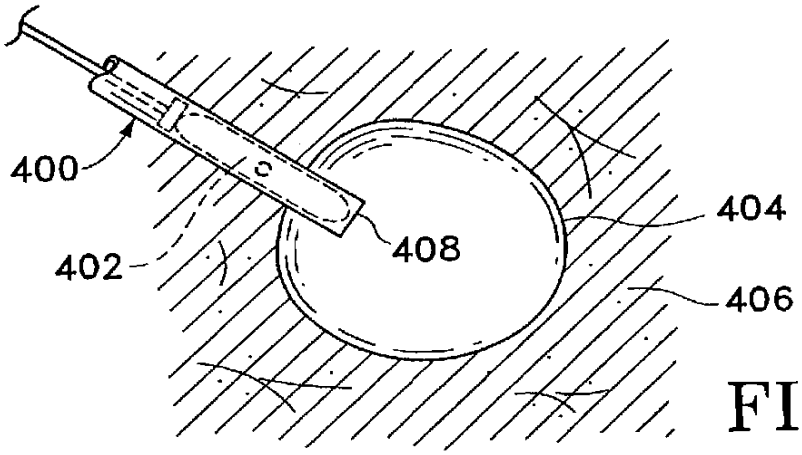


FIG. 4A

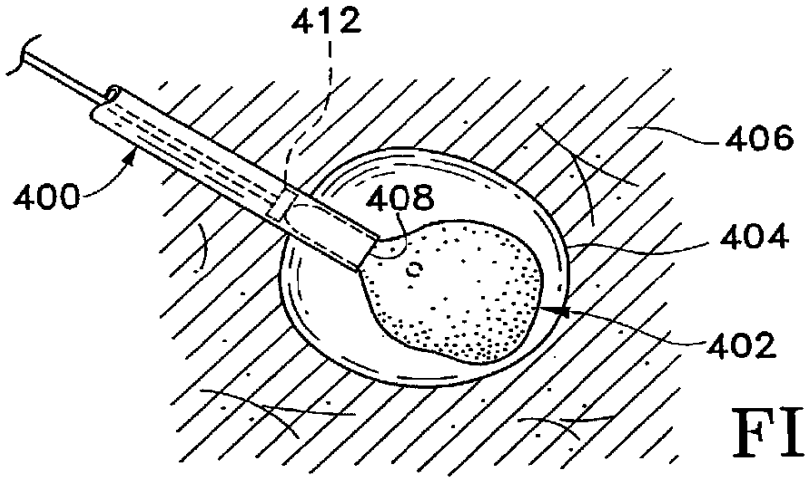


FIG. 4B

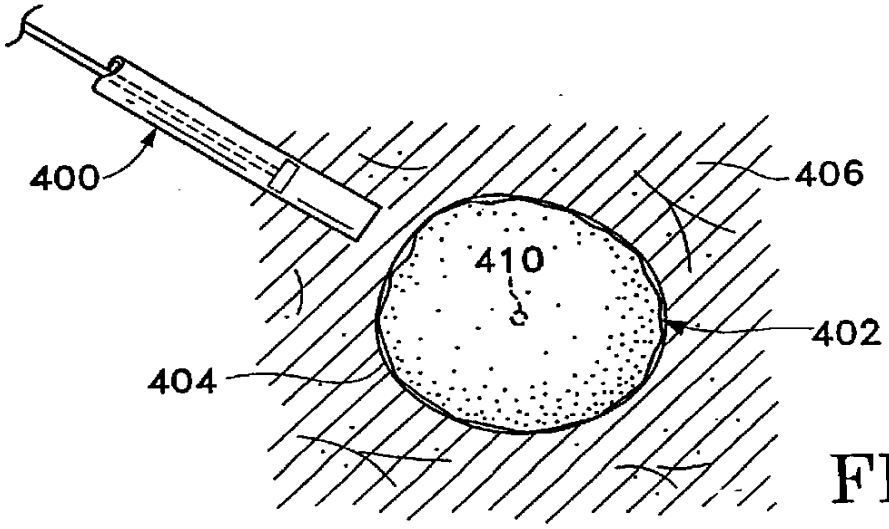


FIG. 4C

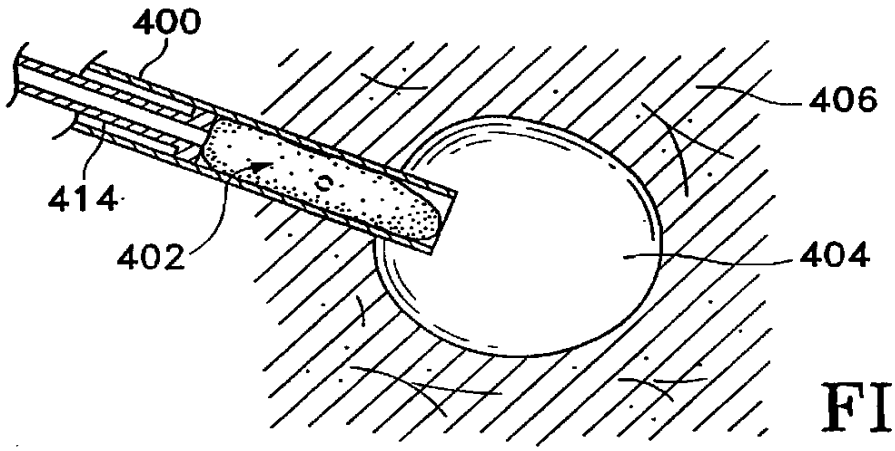


FIG. 4D

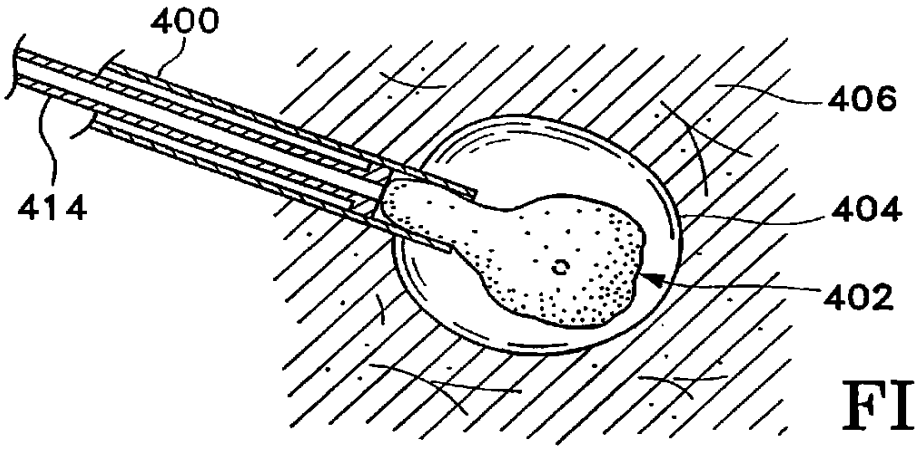


FIG. 4E

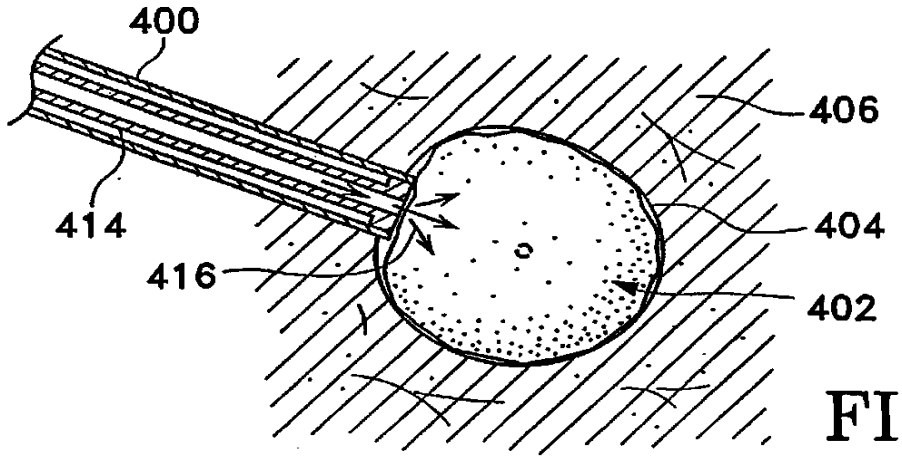


FIG. 4F

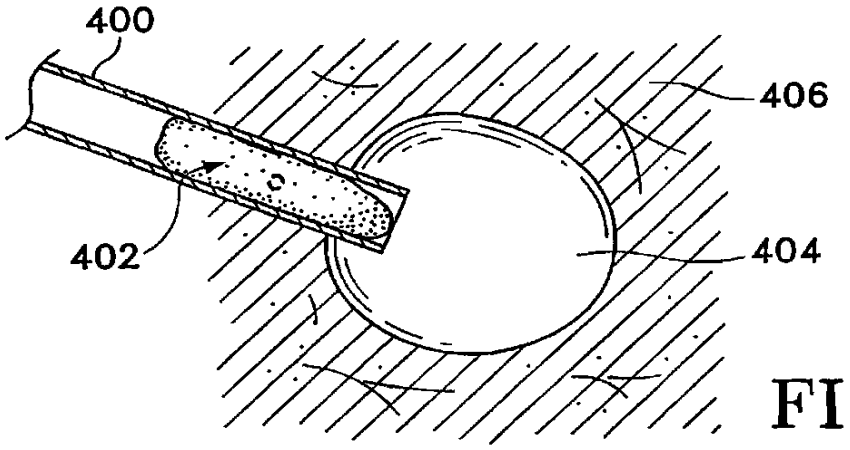


FIG. 4G

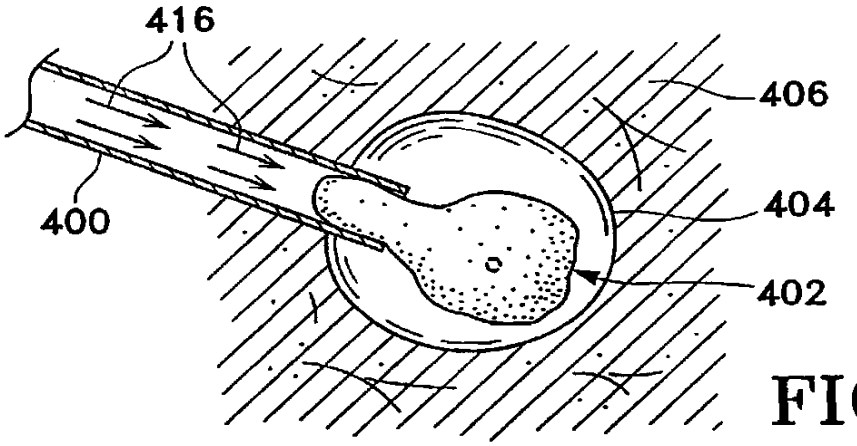


FIG. 4H

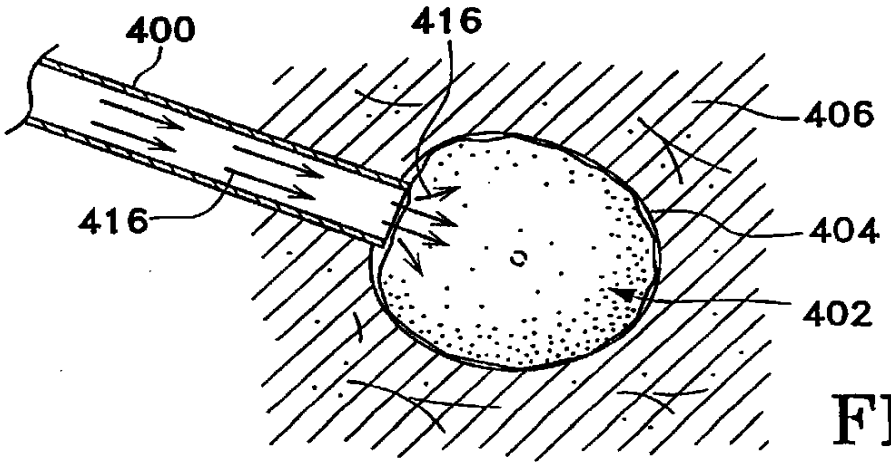


FIG. 4I

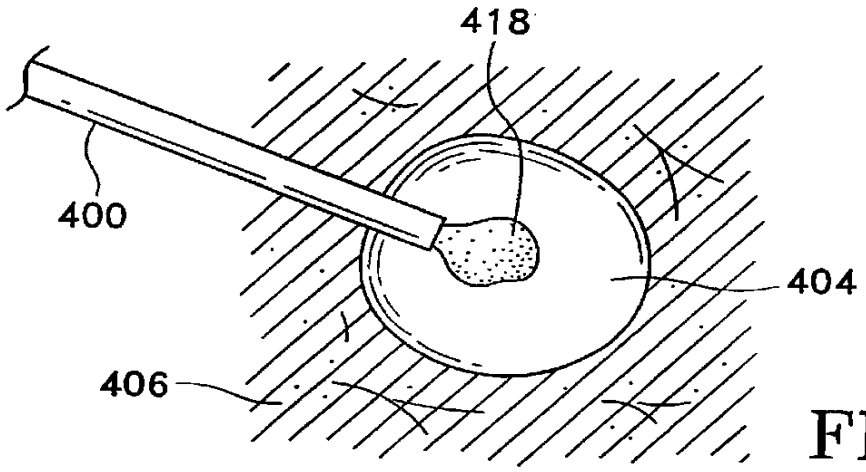


FIG. 4J

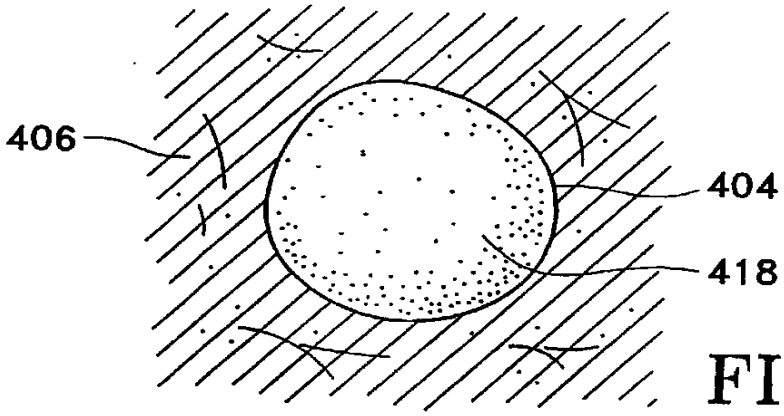


FIG. 4K

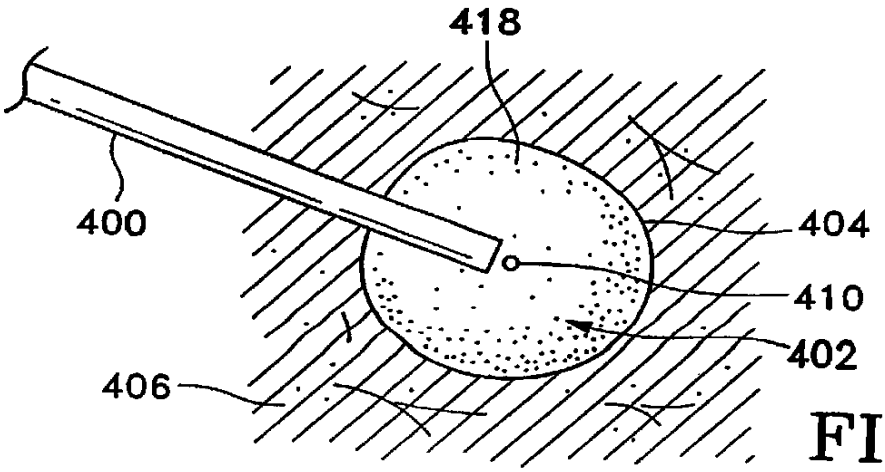


FIG. 4L

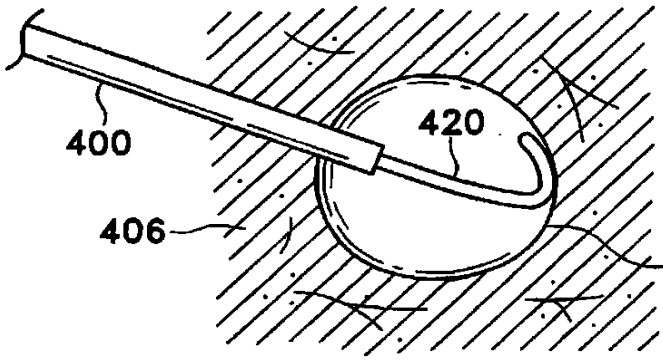


FIG. 4M

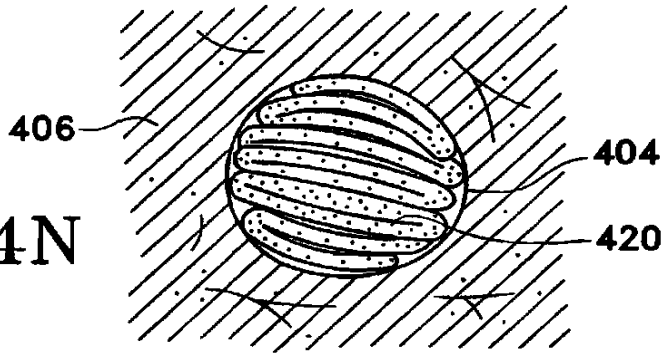


FIG. 4N

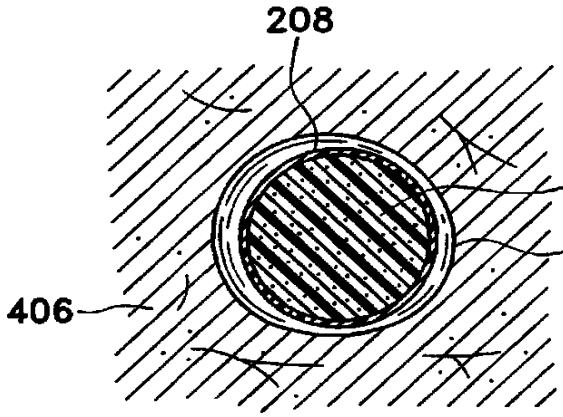


FIG. 4O

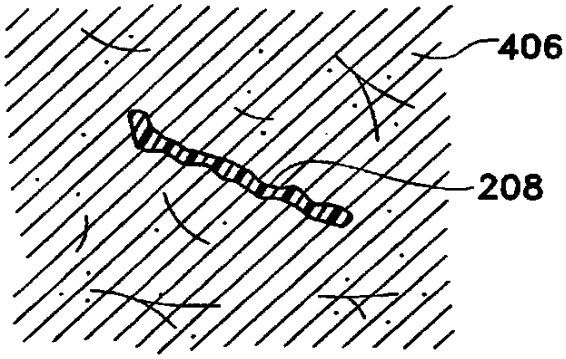


FIG. 4P

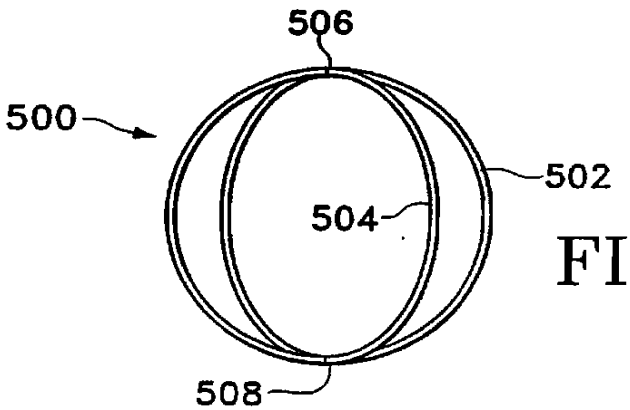


FIG. 5A

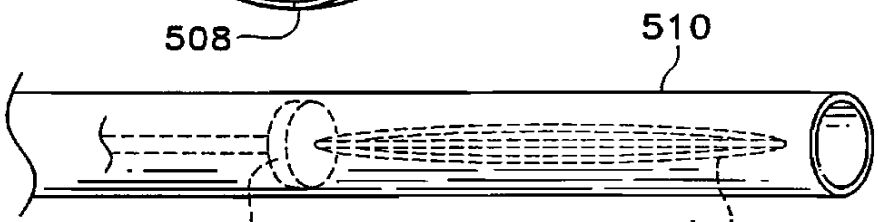


FIG. 5B

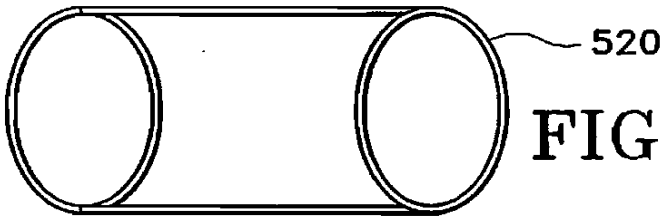
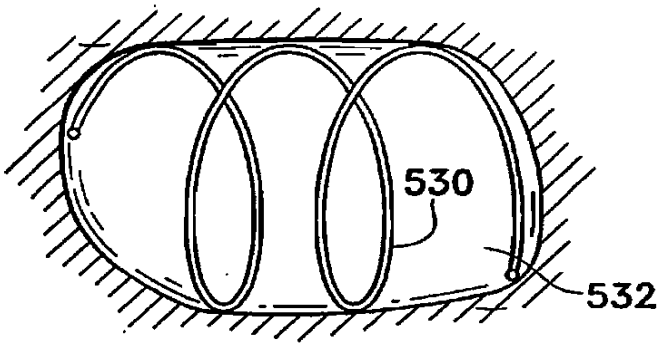


FIG. 5C

FIG. 5D



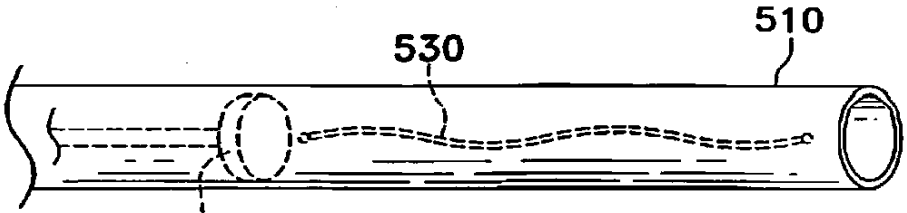


FIG. 5E

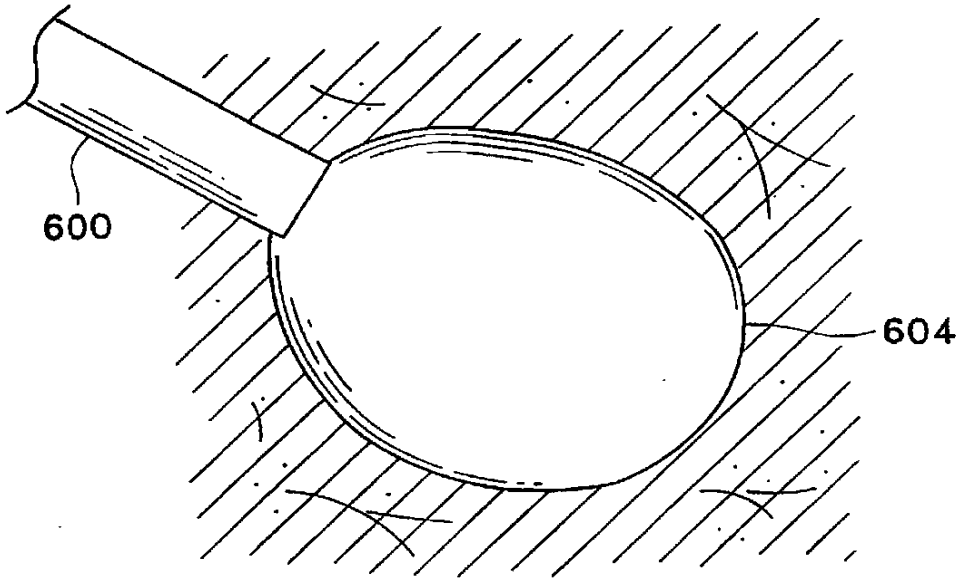


FIG. 6A

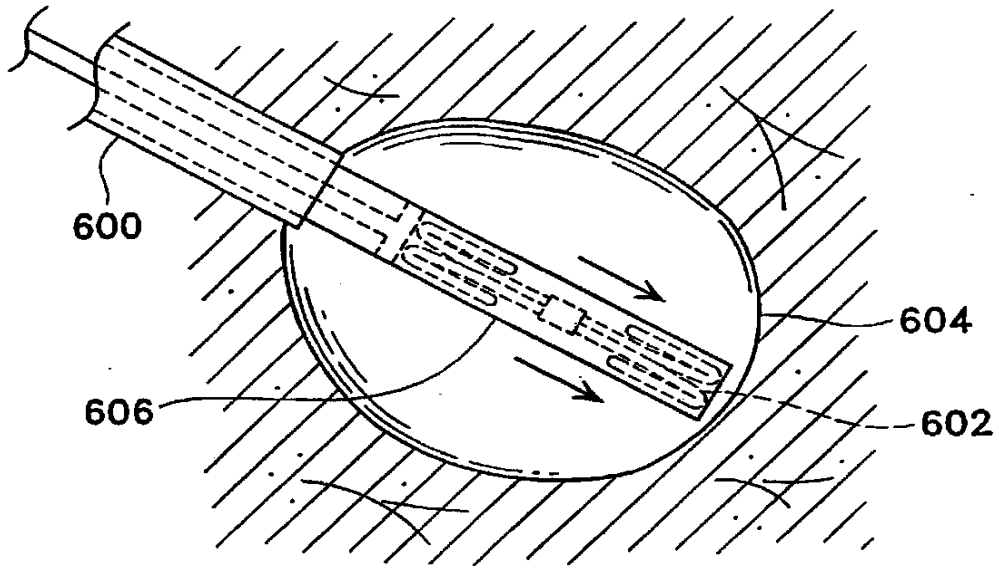


FIG. 6B

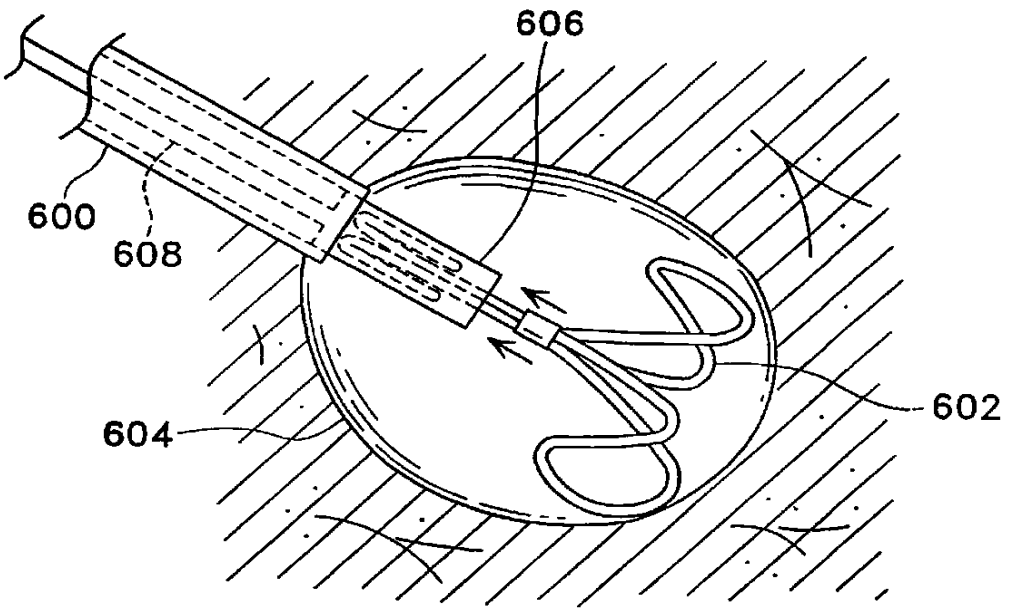


FIG. 6C

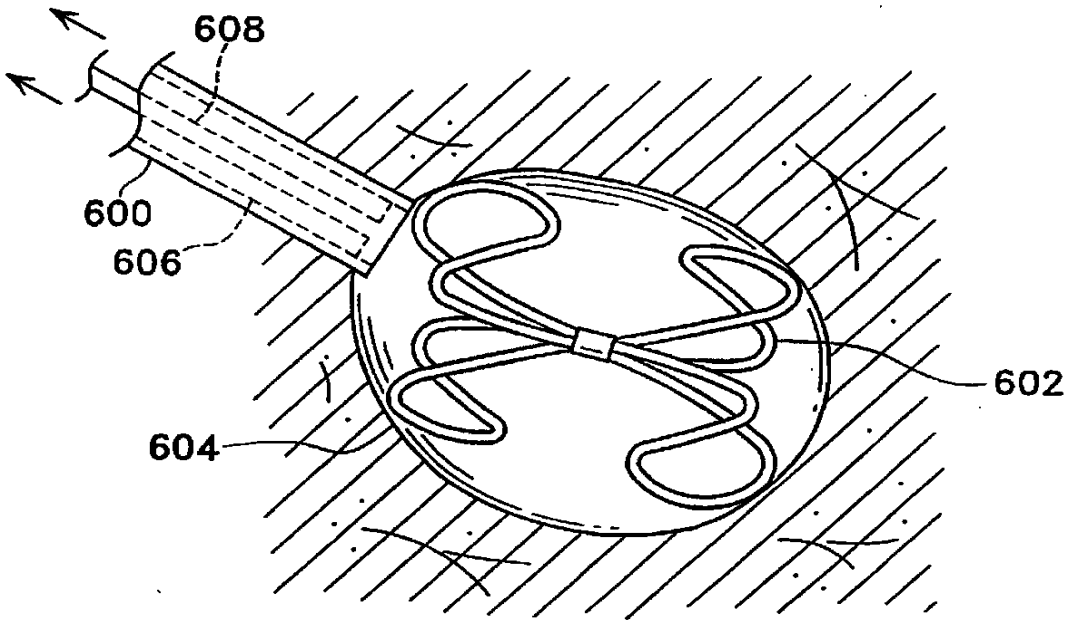


FIG. 6D

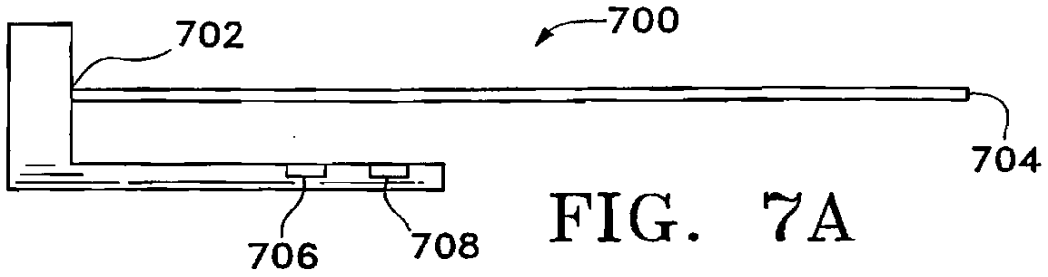


FIG. 7A

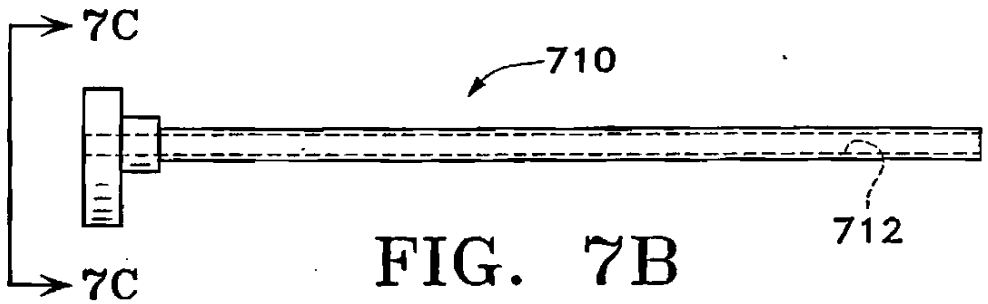


FIG. 7B

FIG. 7C

FIG. 7E

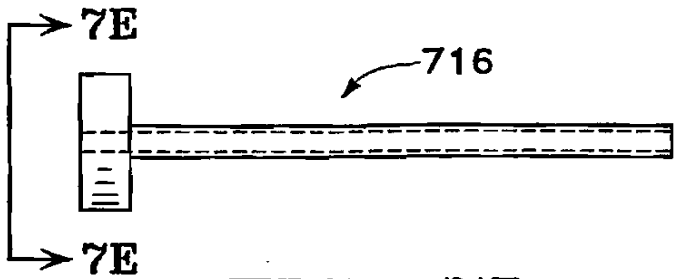


FIG. 7D

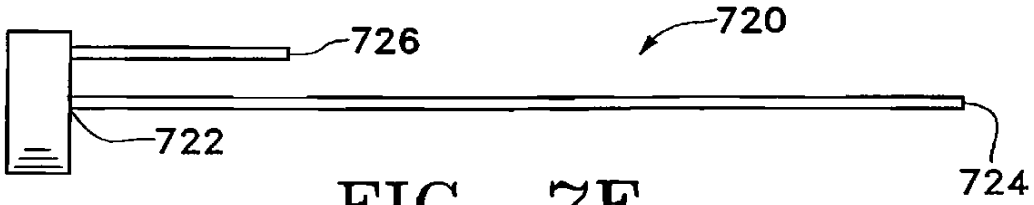


FIG. 7F

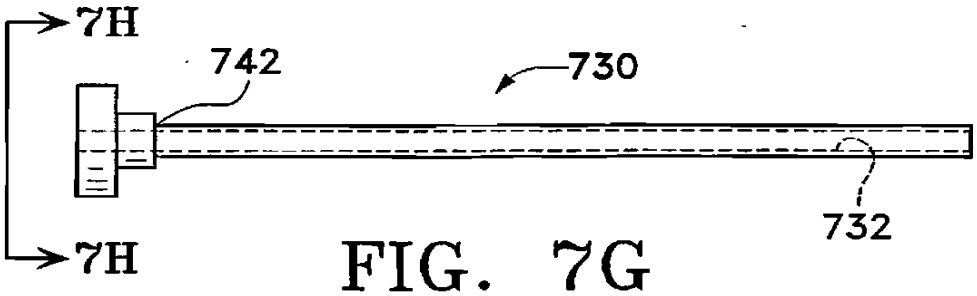


FIG. 7G

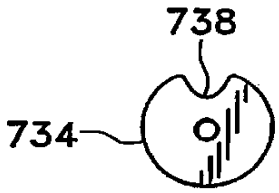


FIG. 7H

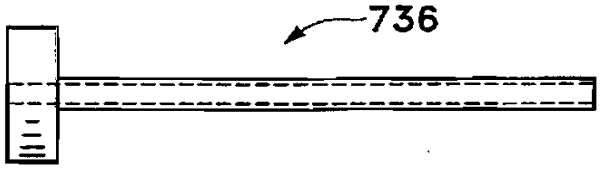


FIG. 7I

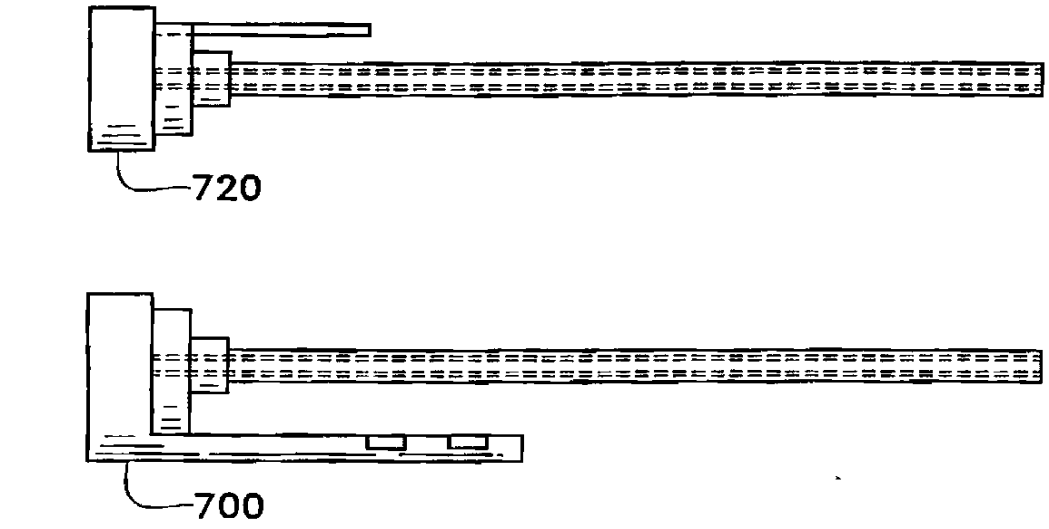


FIG. 7J

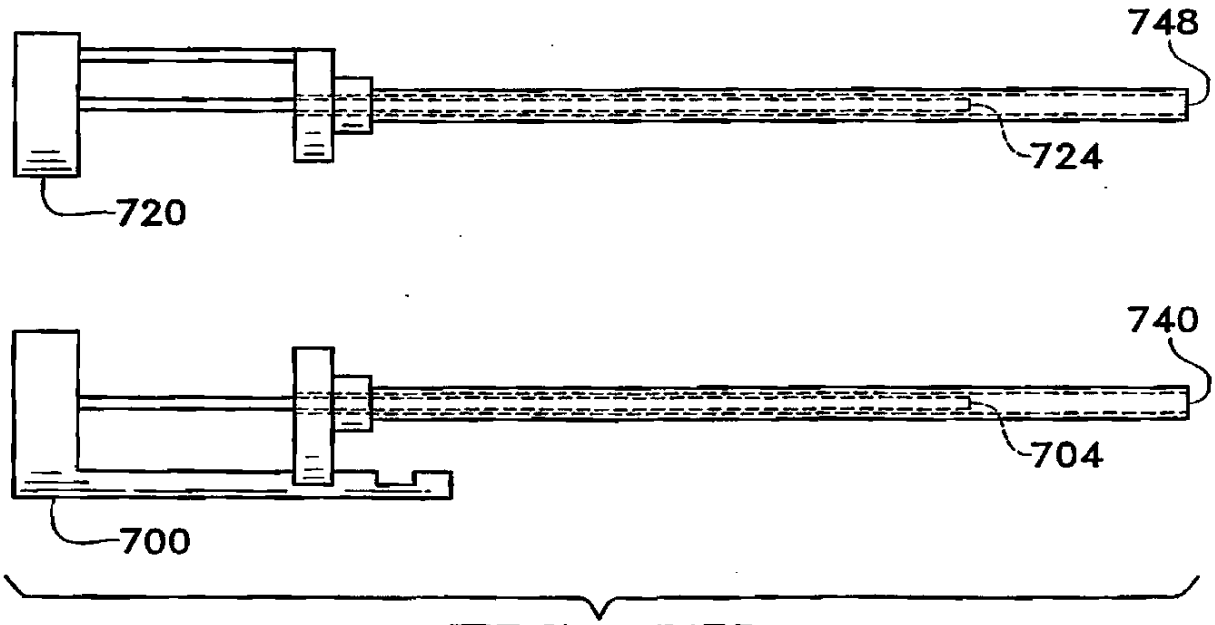


FIG. 7K

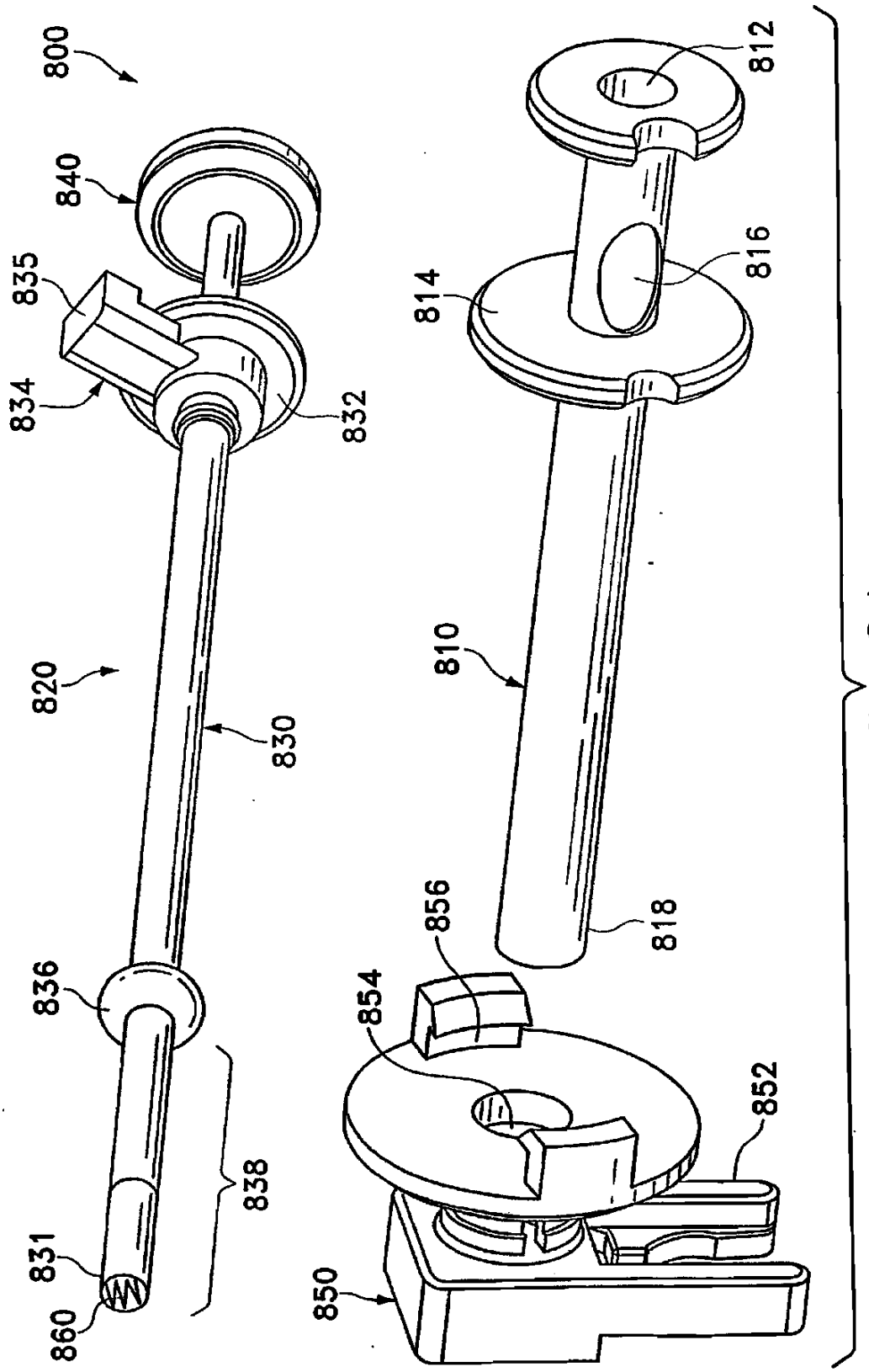


FIG. 8A

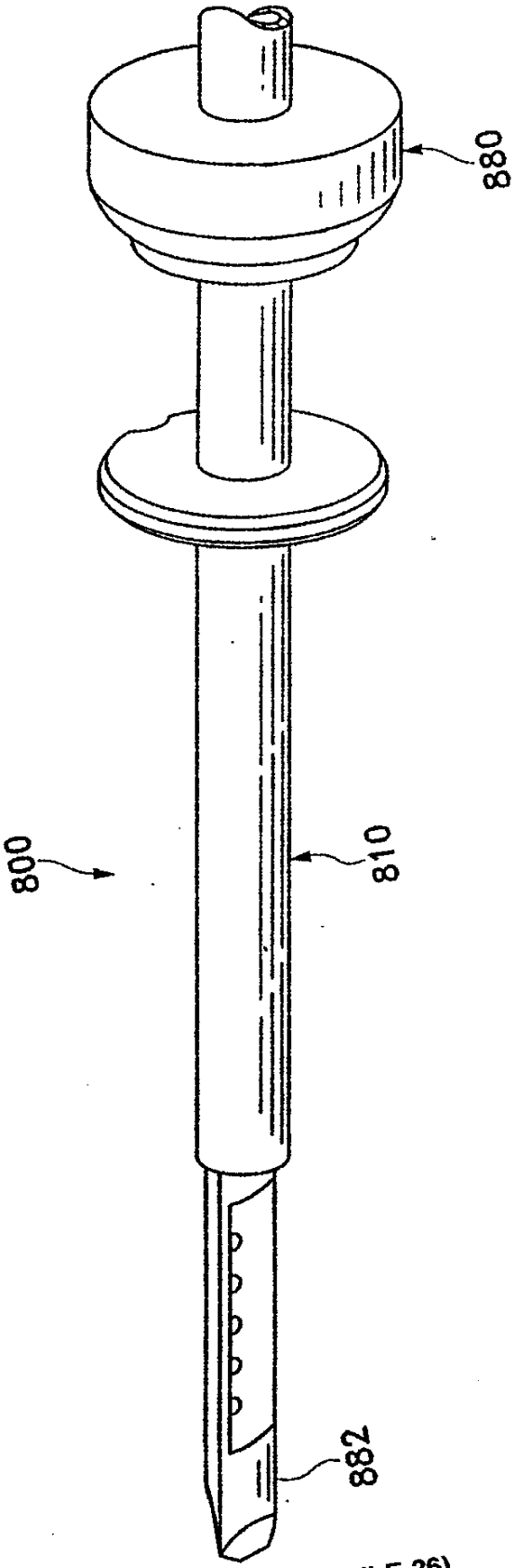


FIG. 8B

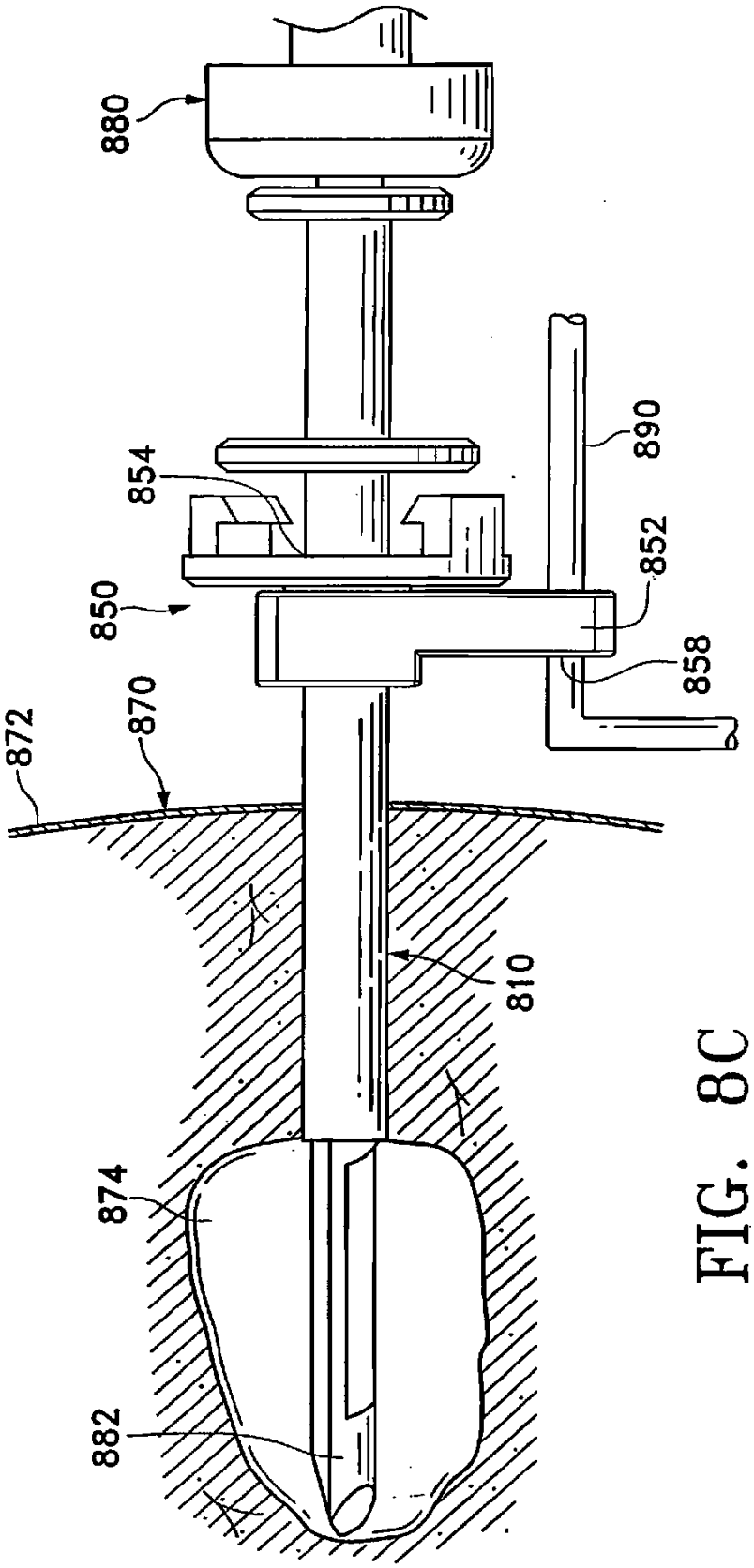


FIG. 8C

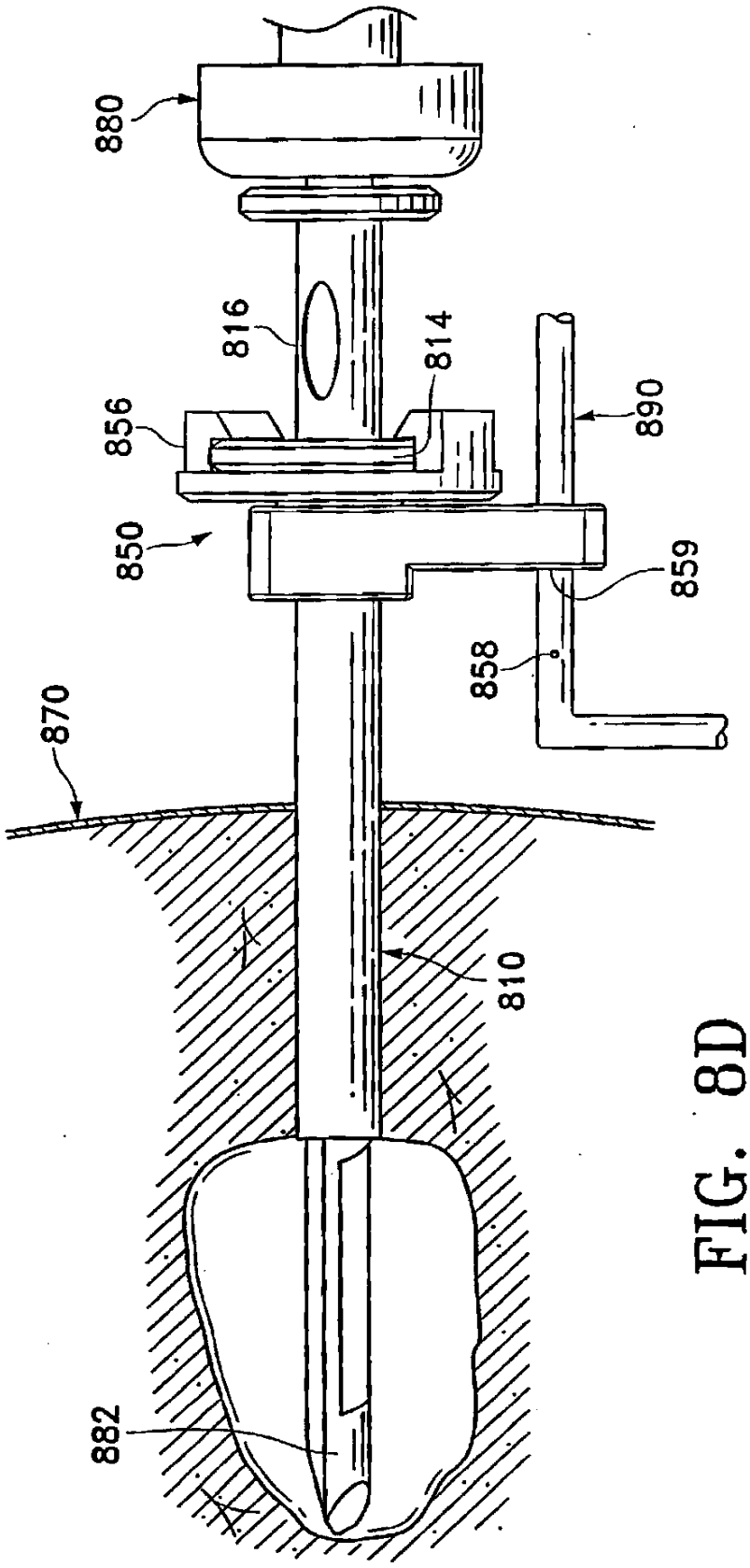


FIG. 8D

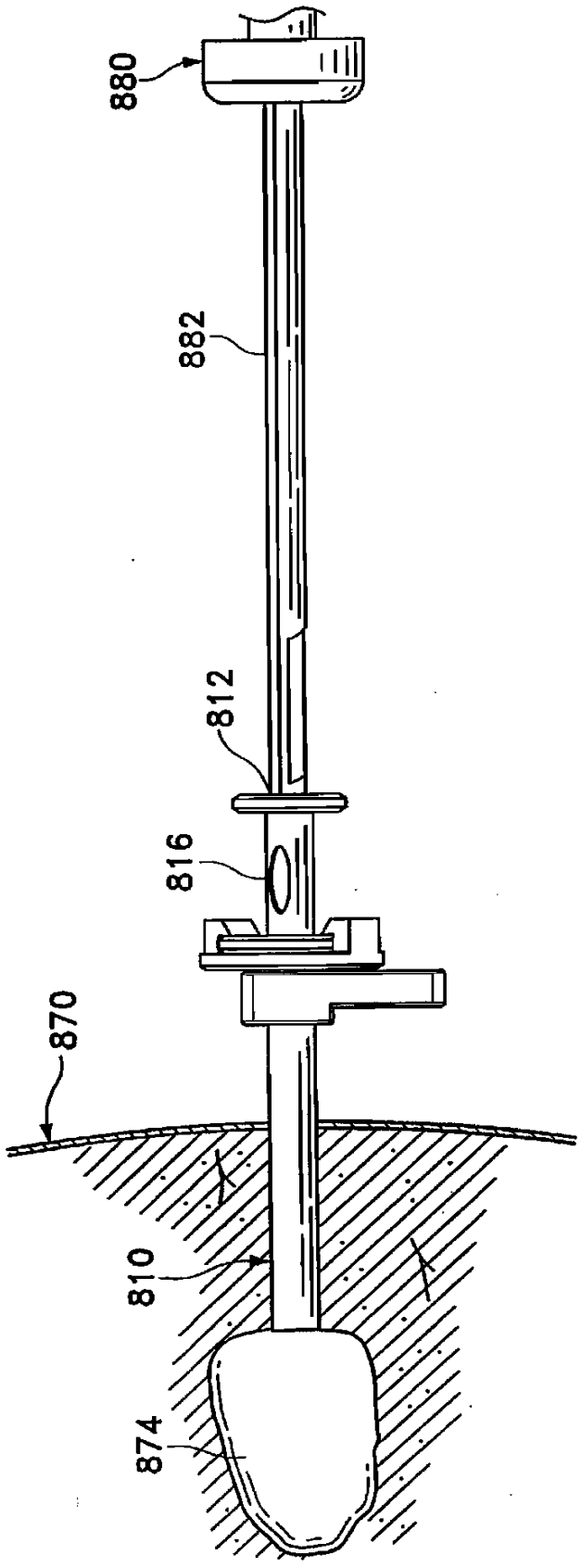


FIG. 8E

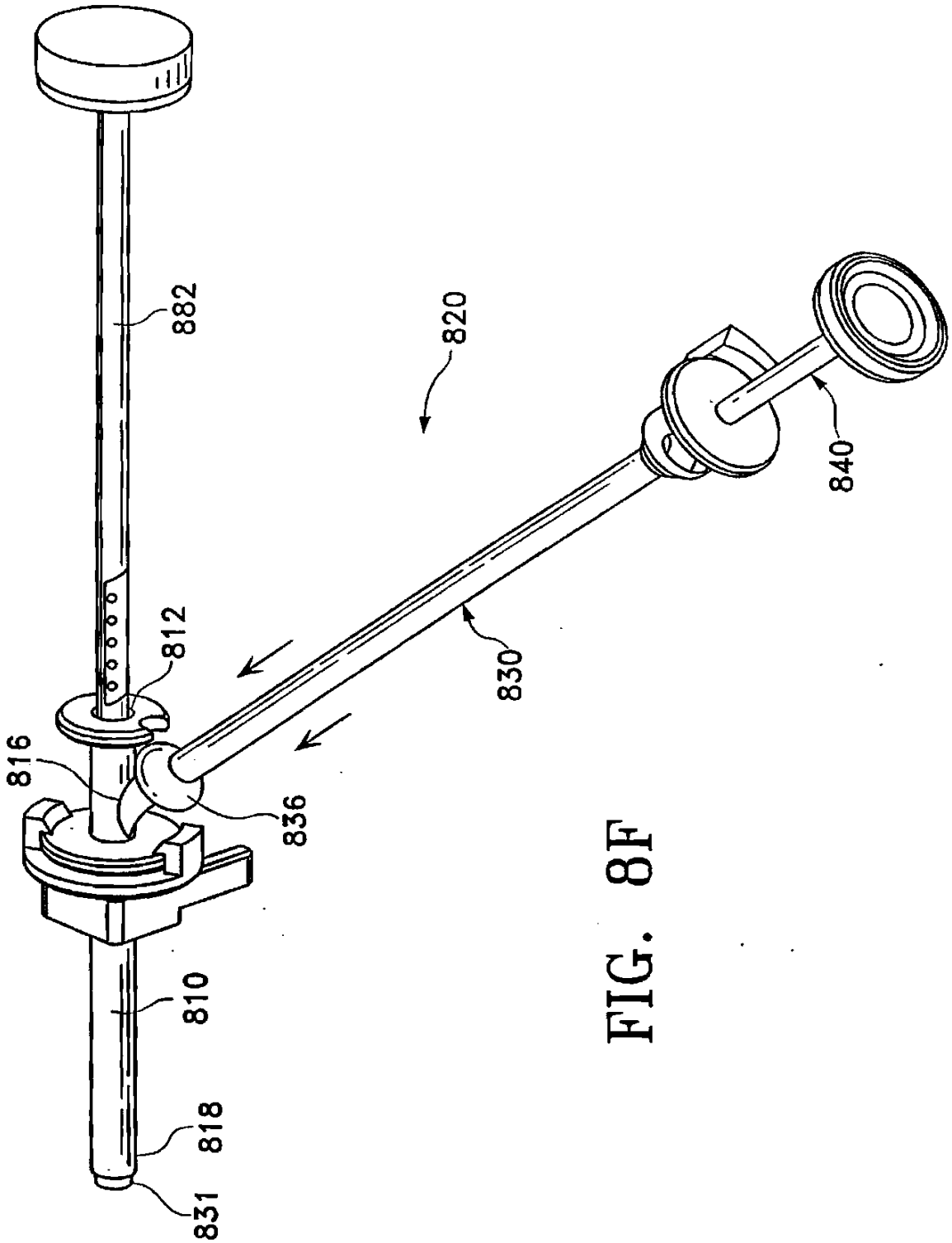


FIG. 8F

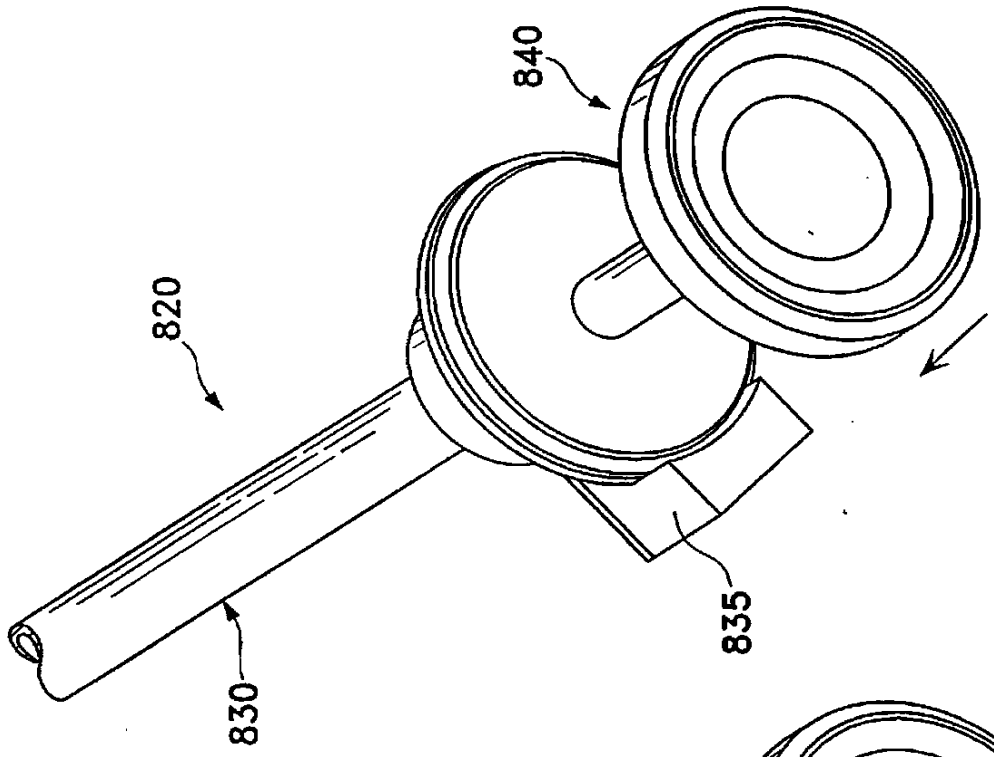


FIG. 8H

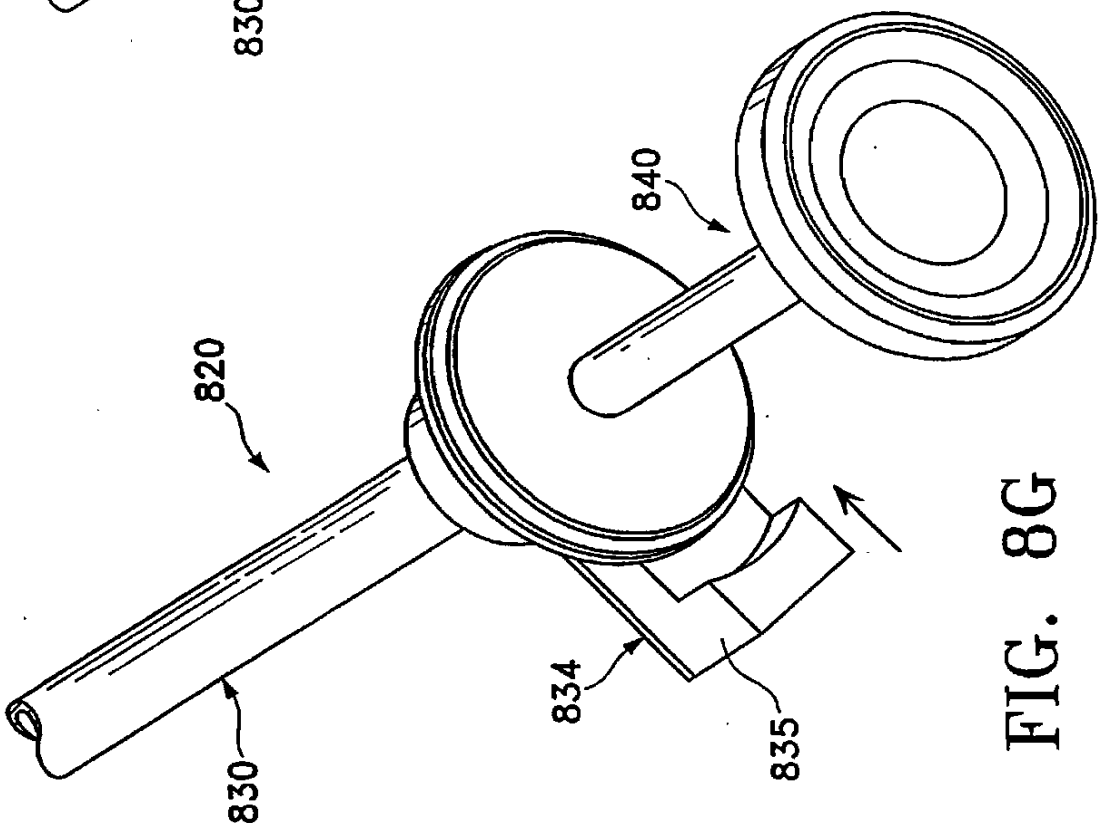


FIG. 8G

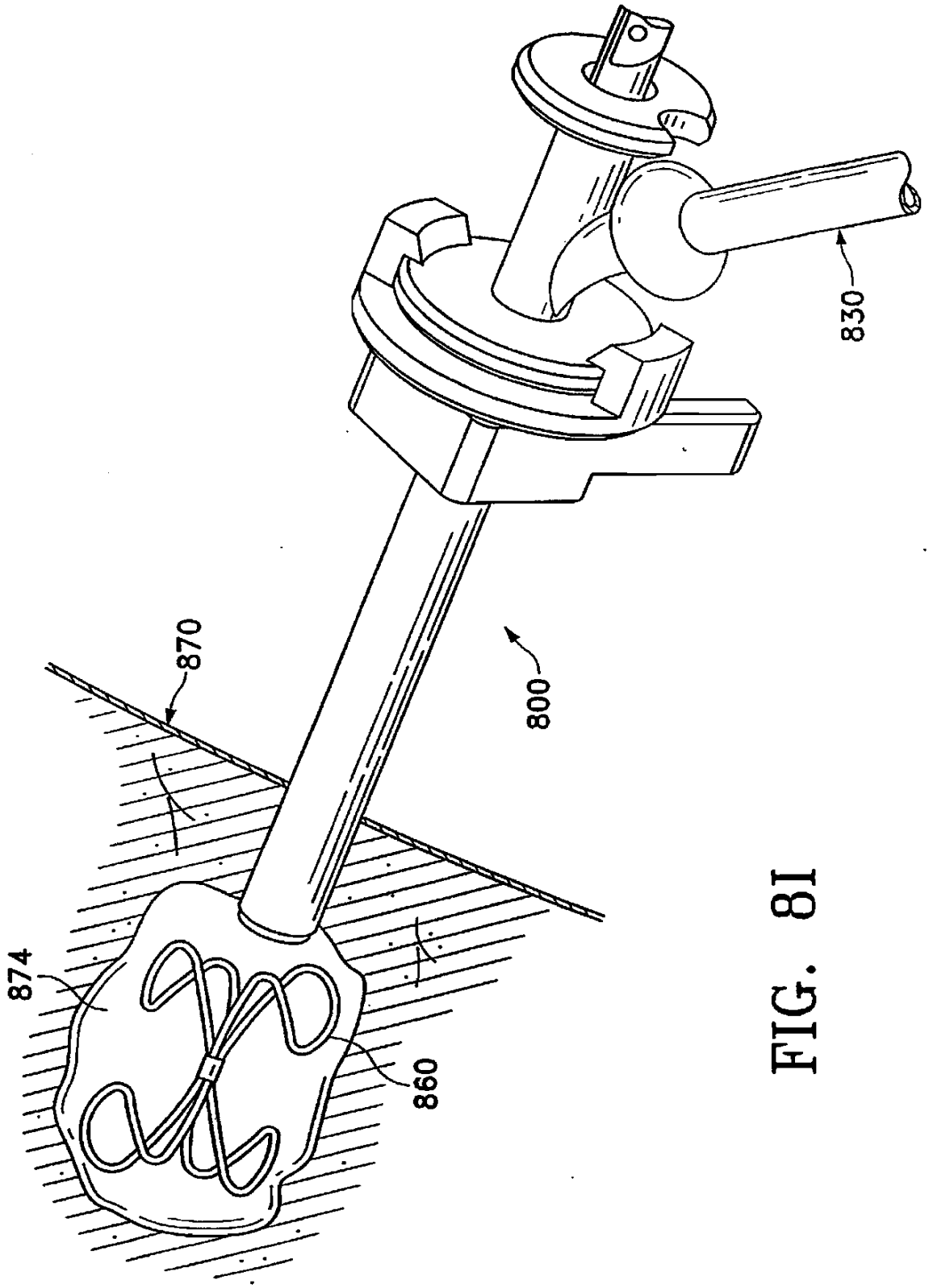


FIG. 81

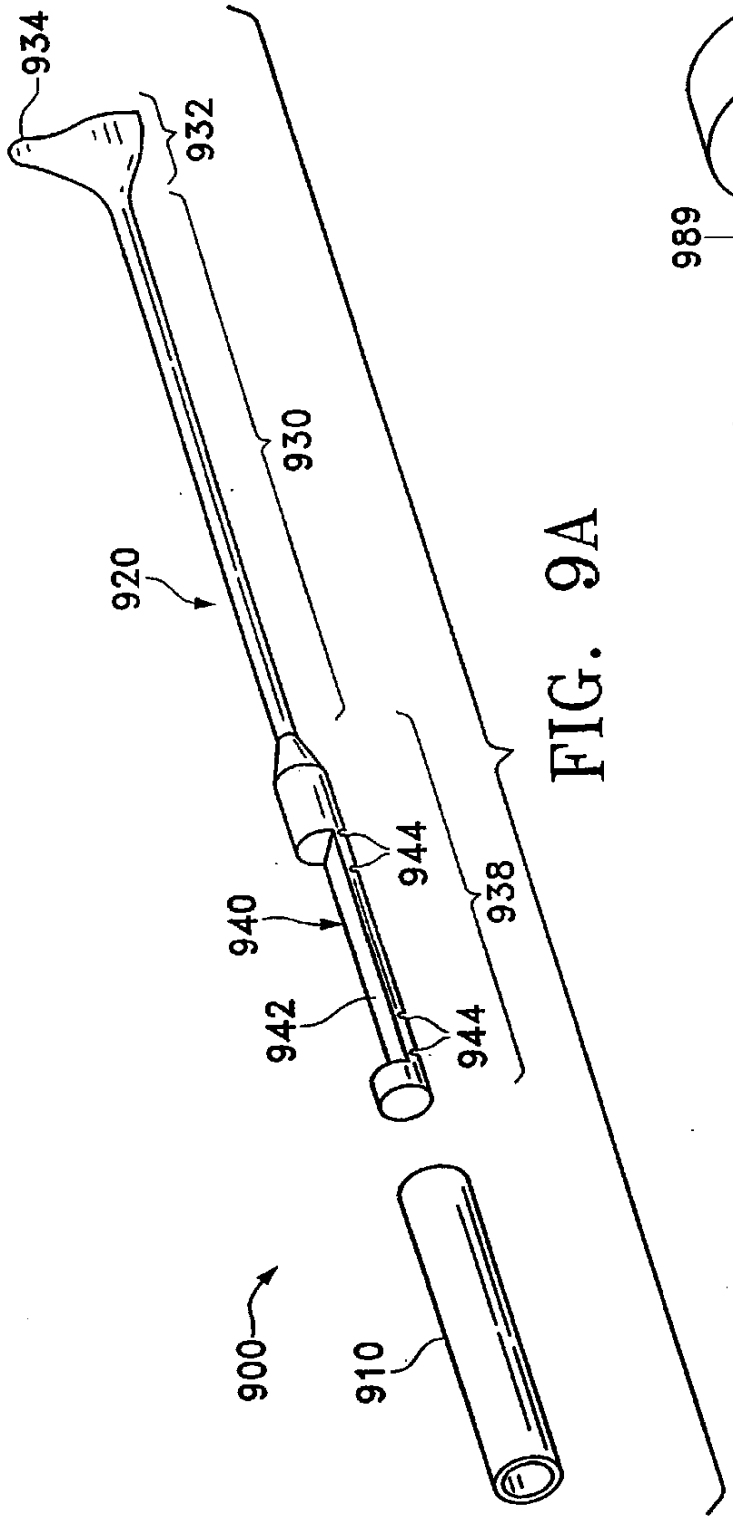


FIG. 9A

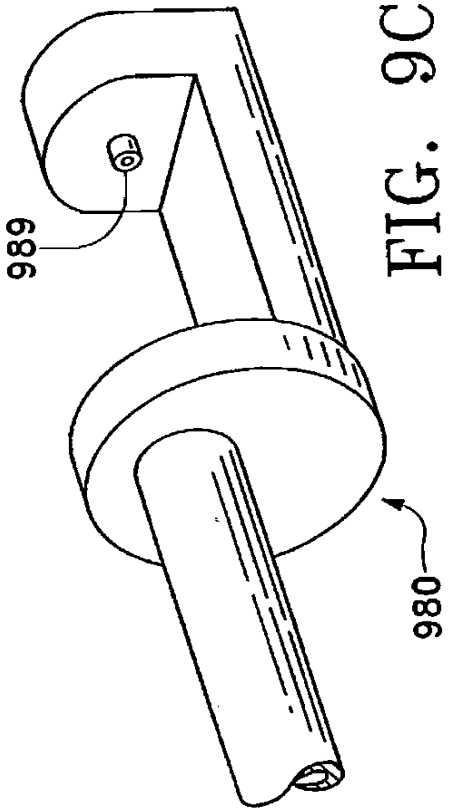


FIG. 9C

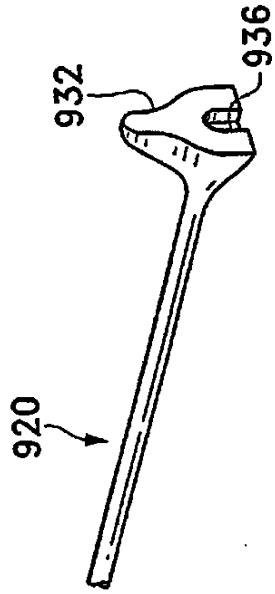
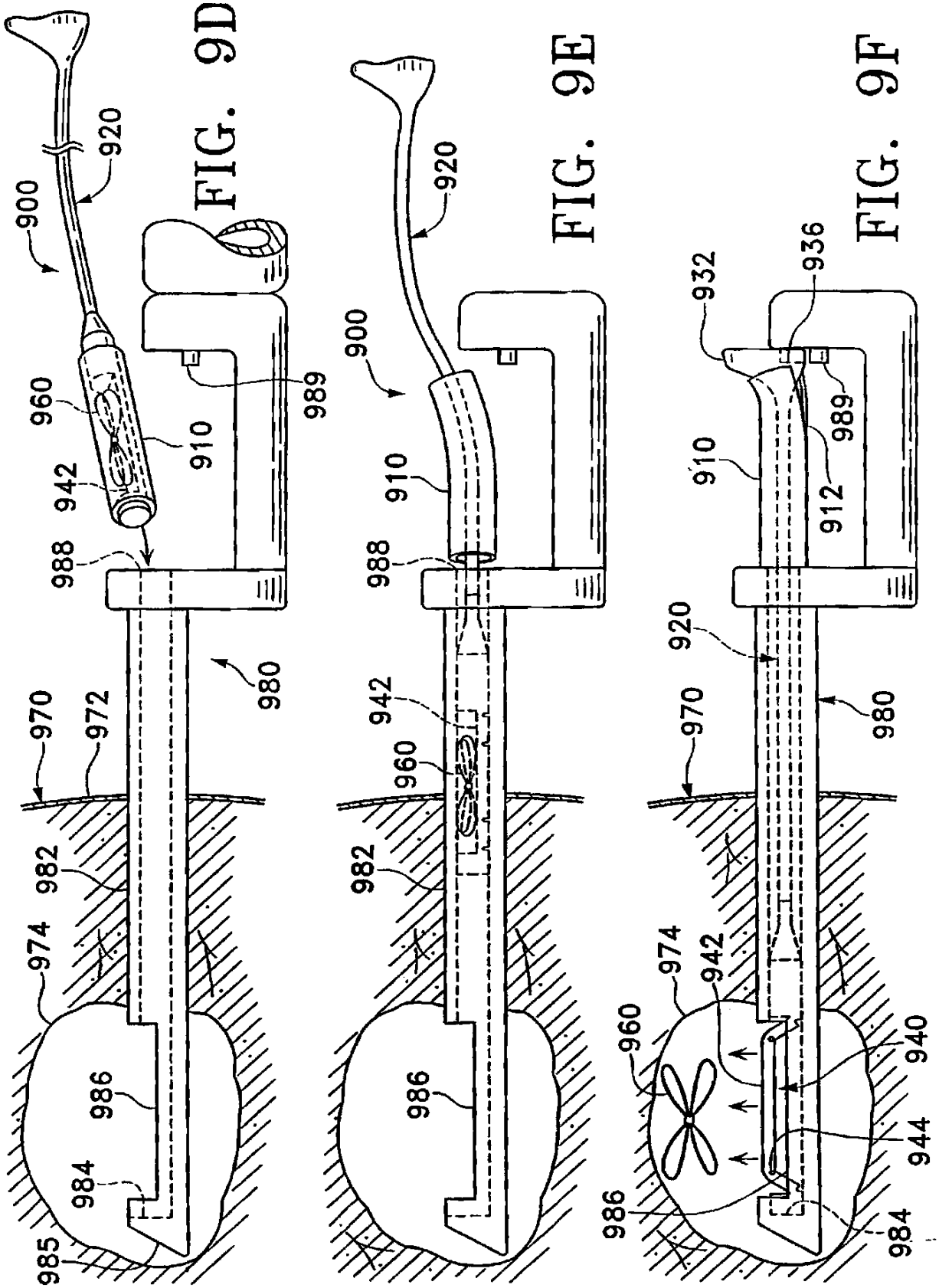


FIG. 9B



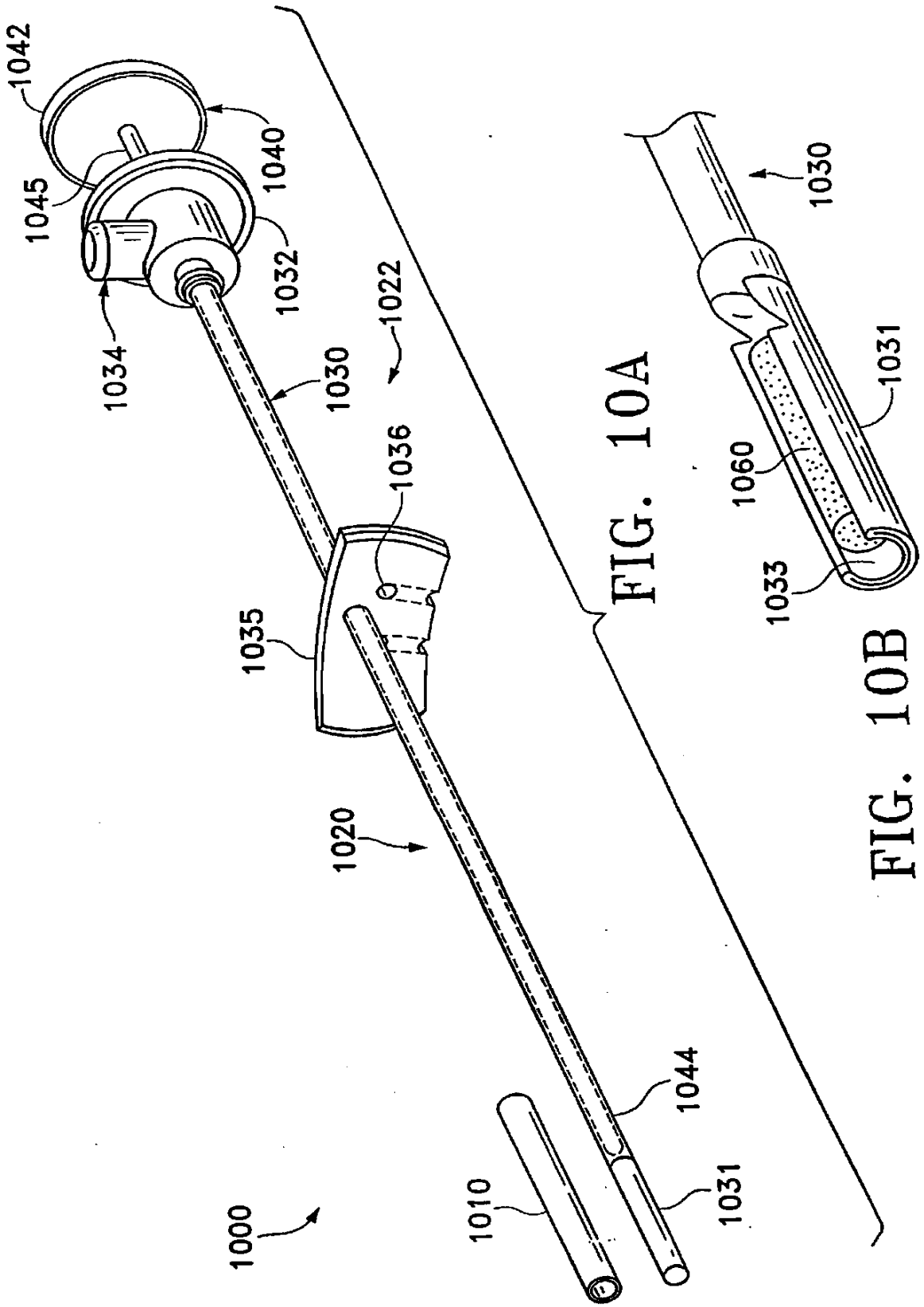


FIG. 10A

FIG. 10B

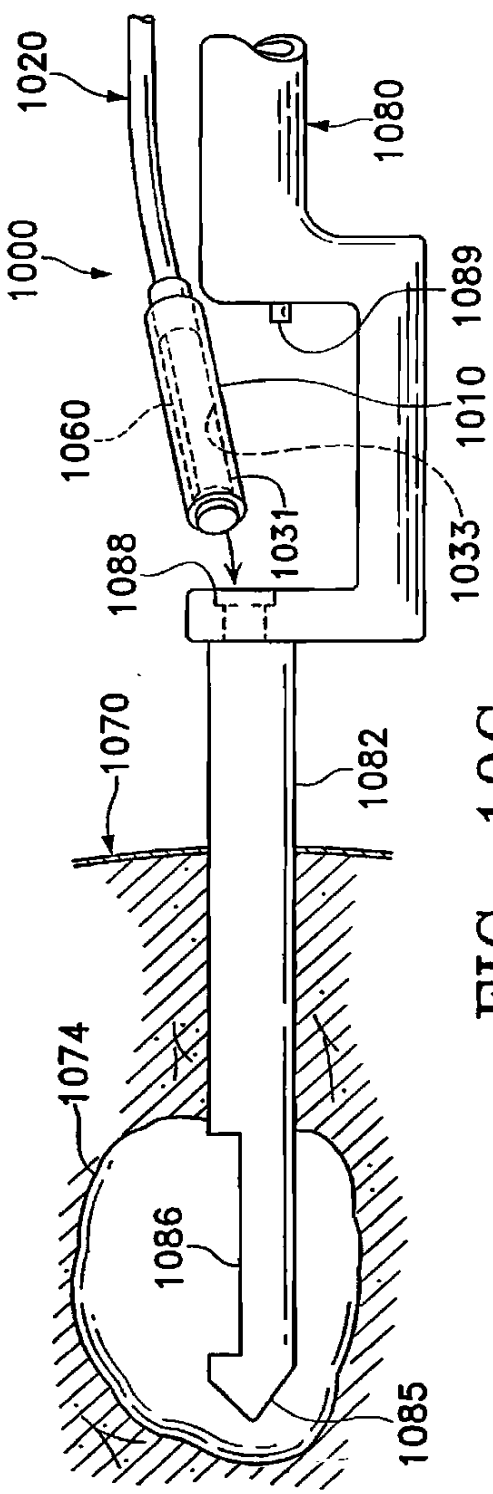


FIG. 10C

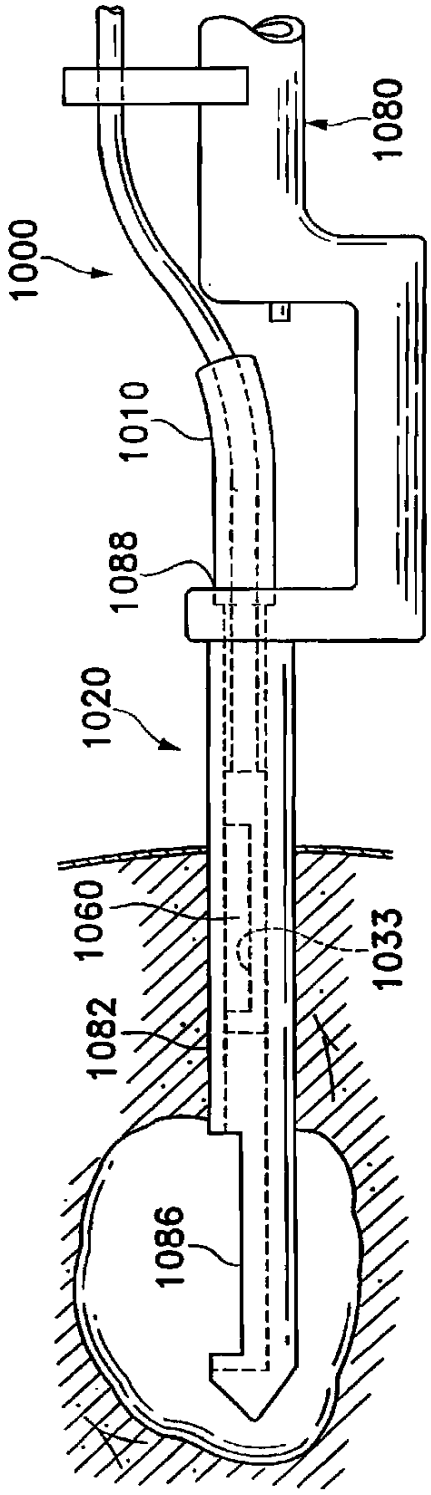


FIG. 10D

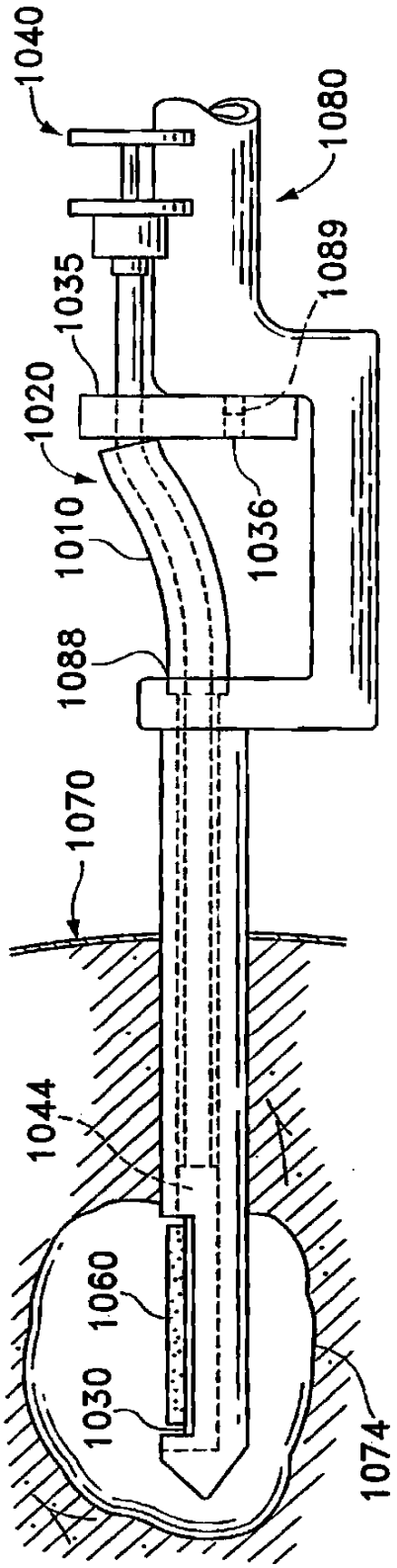


FIG. 10E

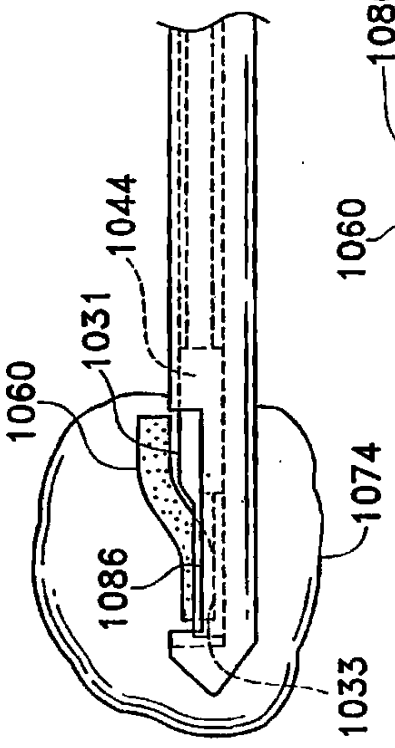


FIG. 10F

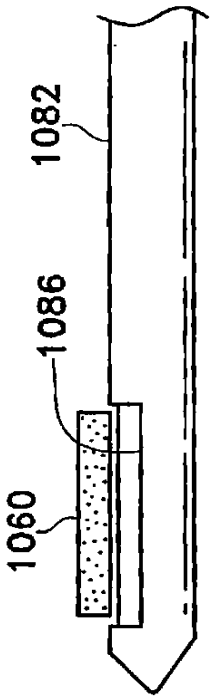


FIG. 10G

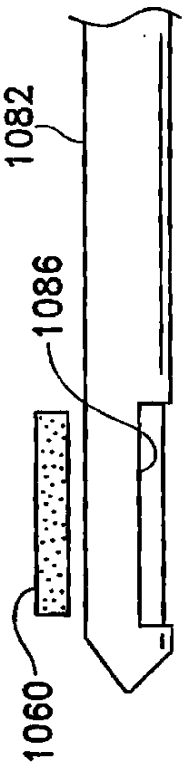


FIG. 10H

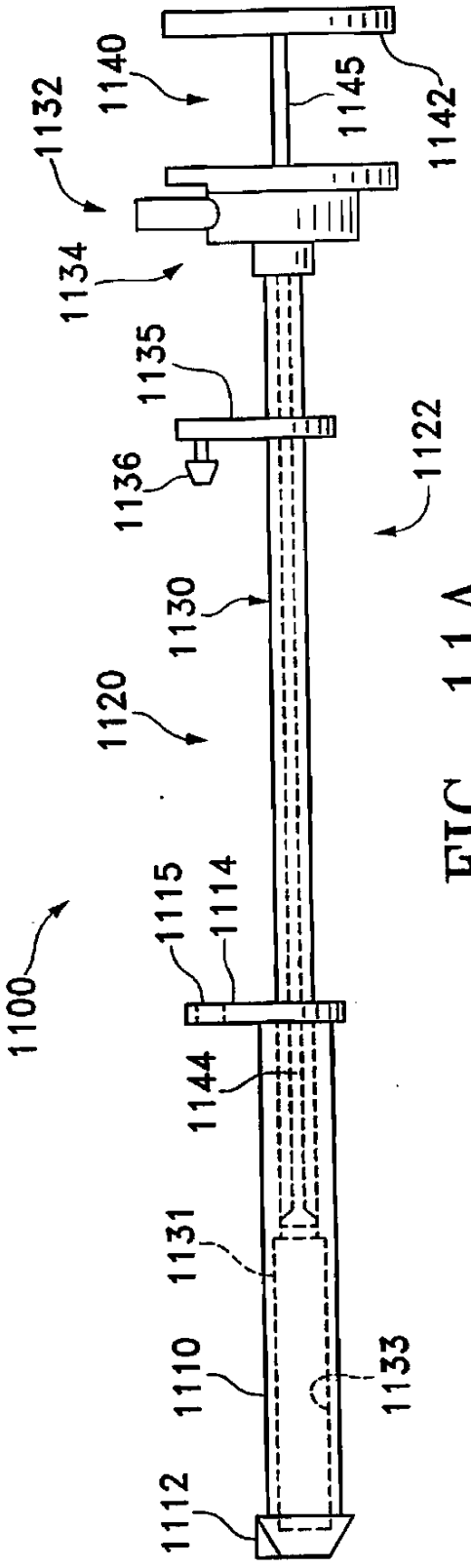


FIG. 11A

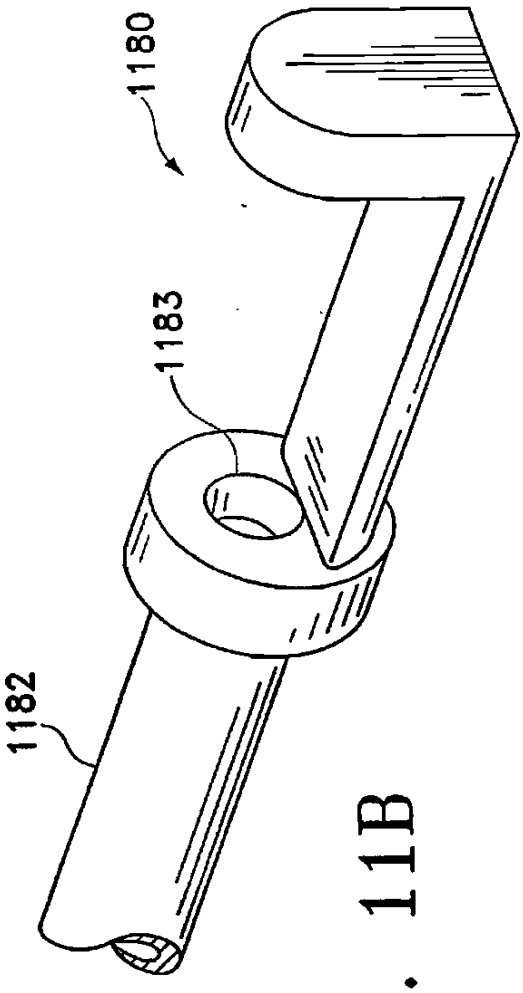


FIG. 11B

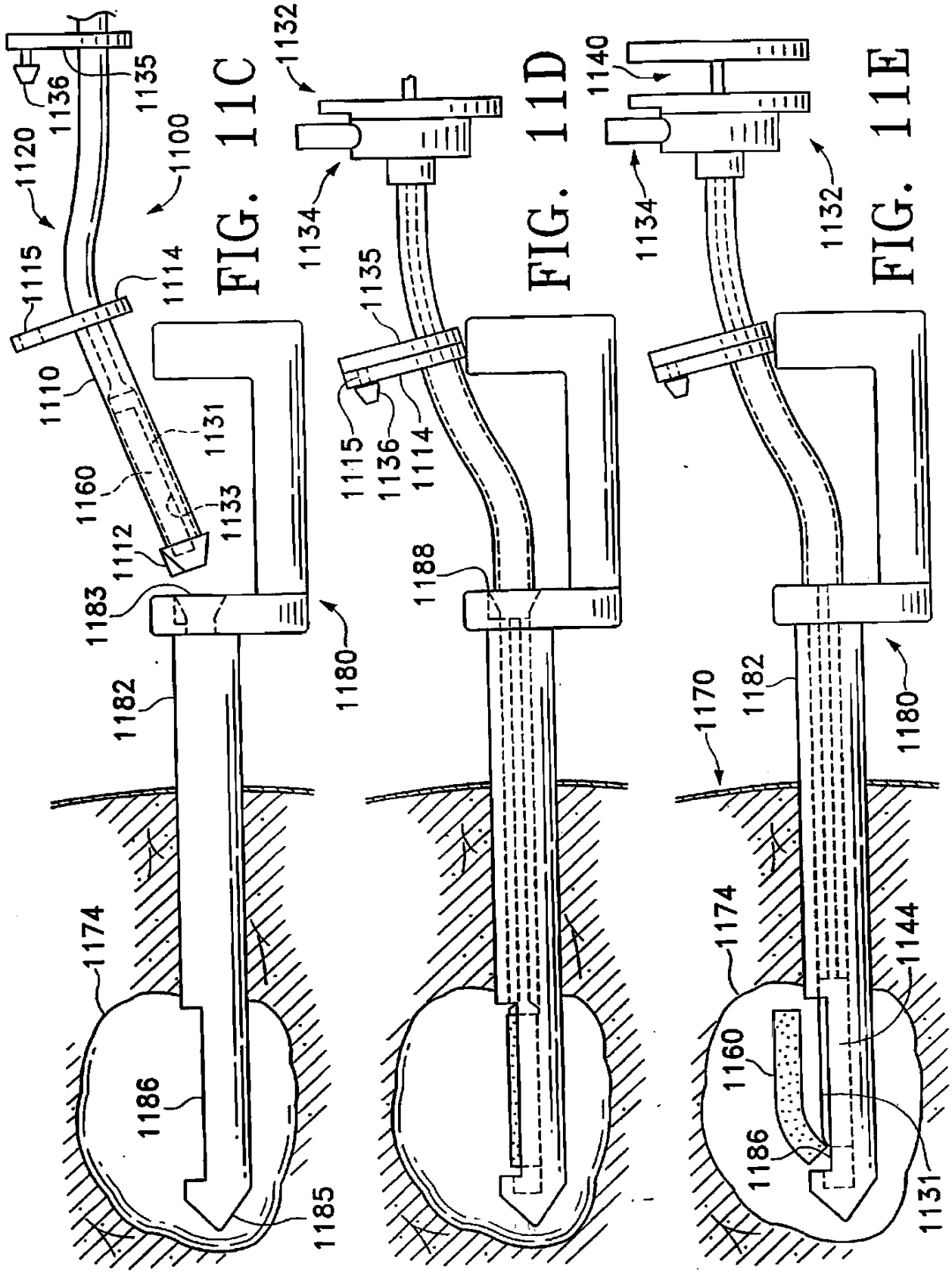


FIG. 11C

FIG. 11D

FIG. 11E

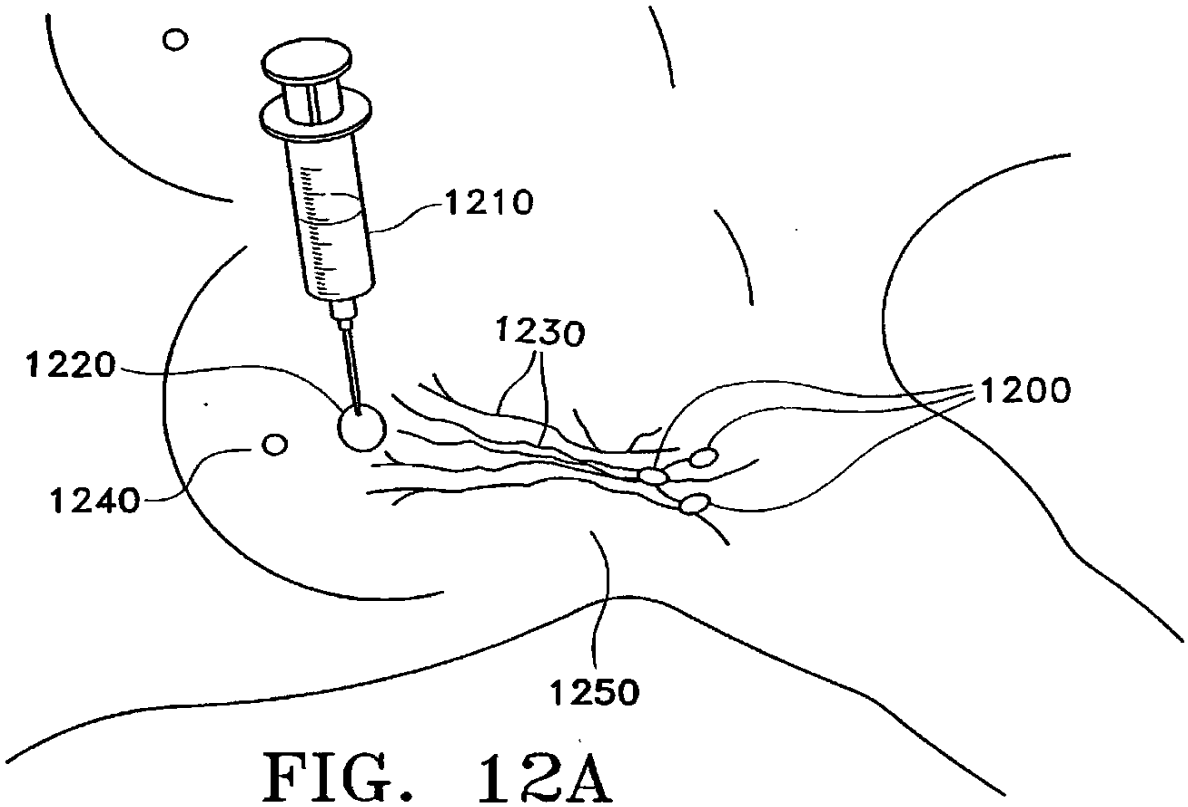
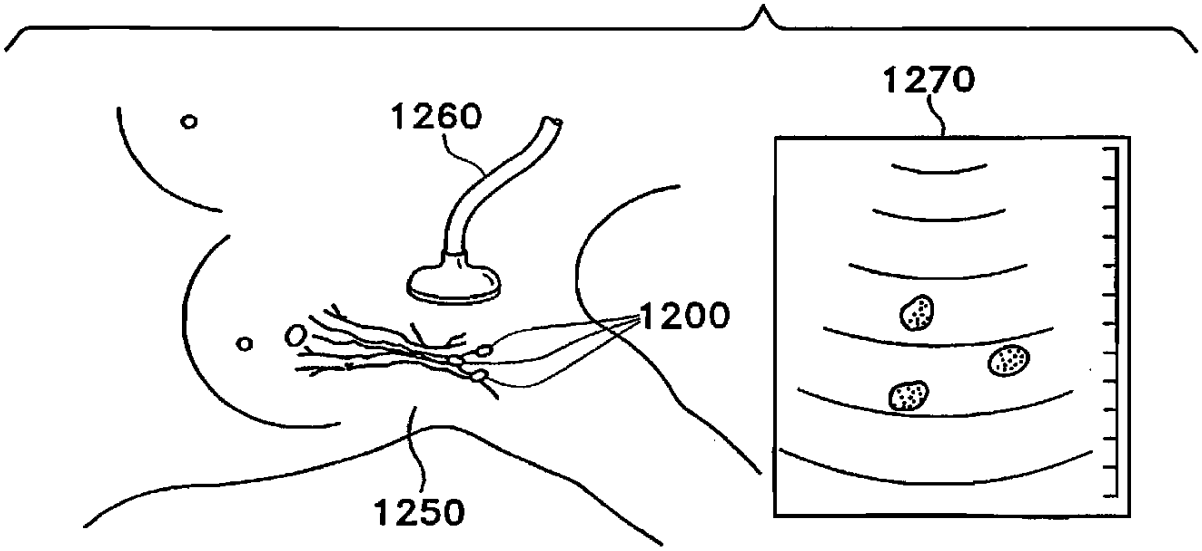


FIG. 12A

FIG. 12B



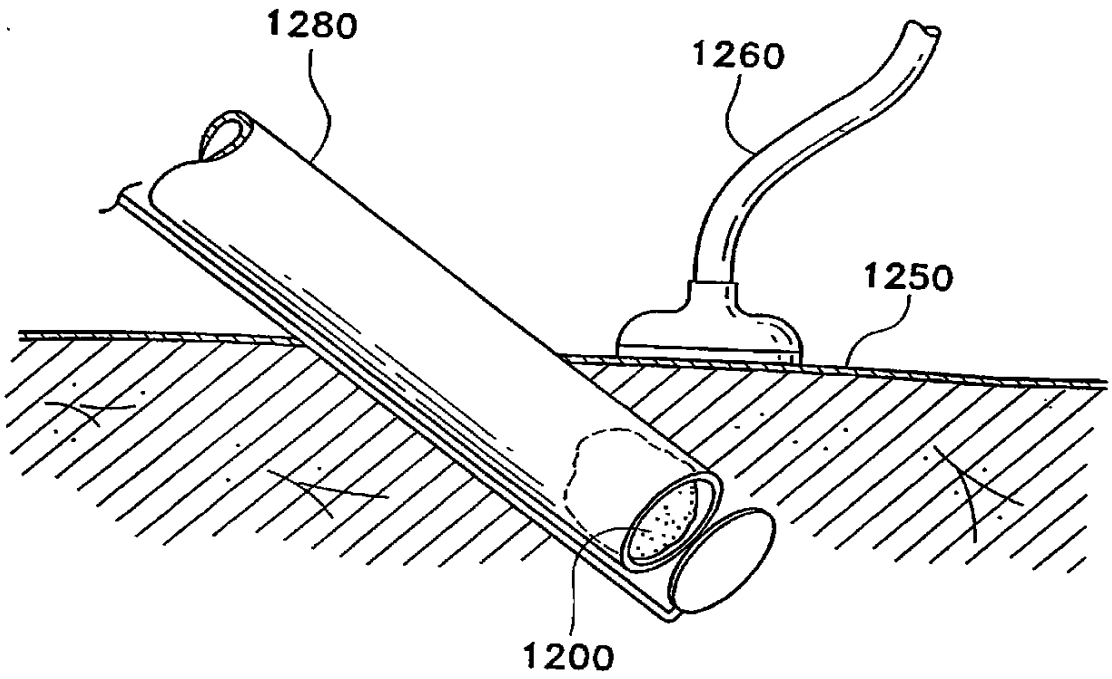


FIG. 12C

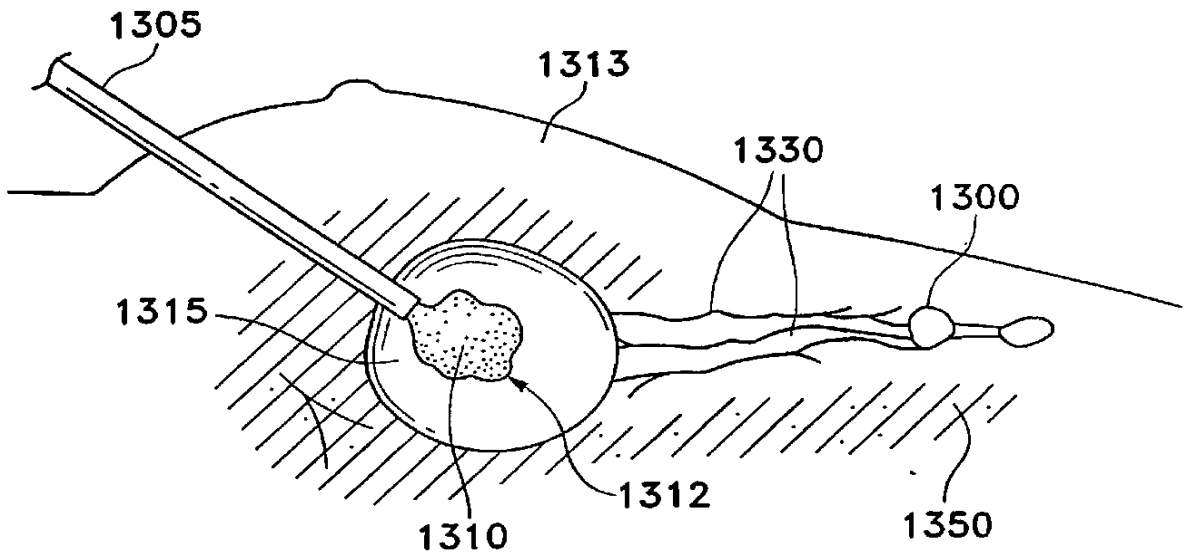


FIG. 13A

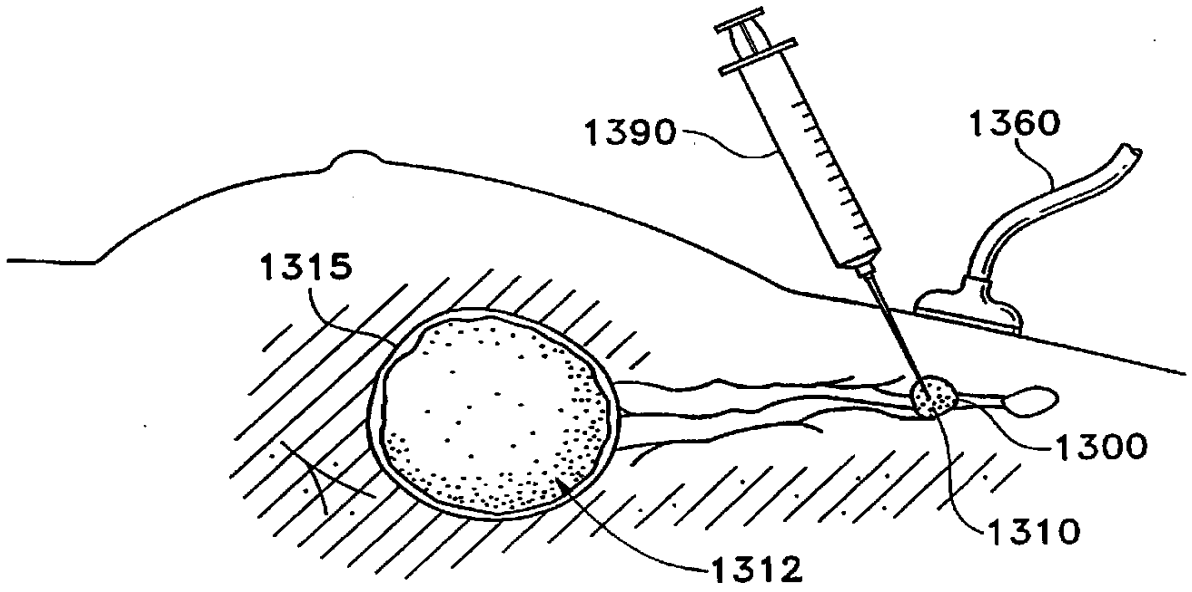


FIG. 13B

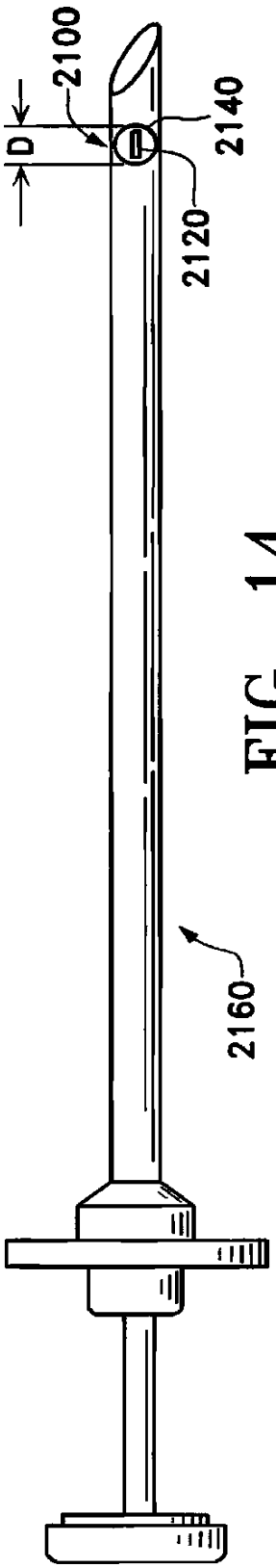


FIG. 14

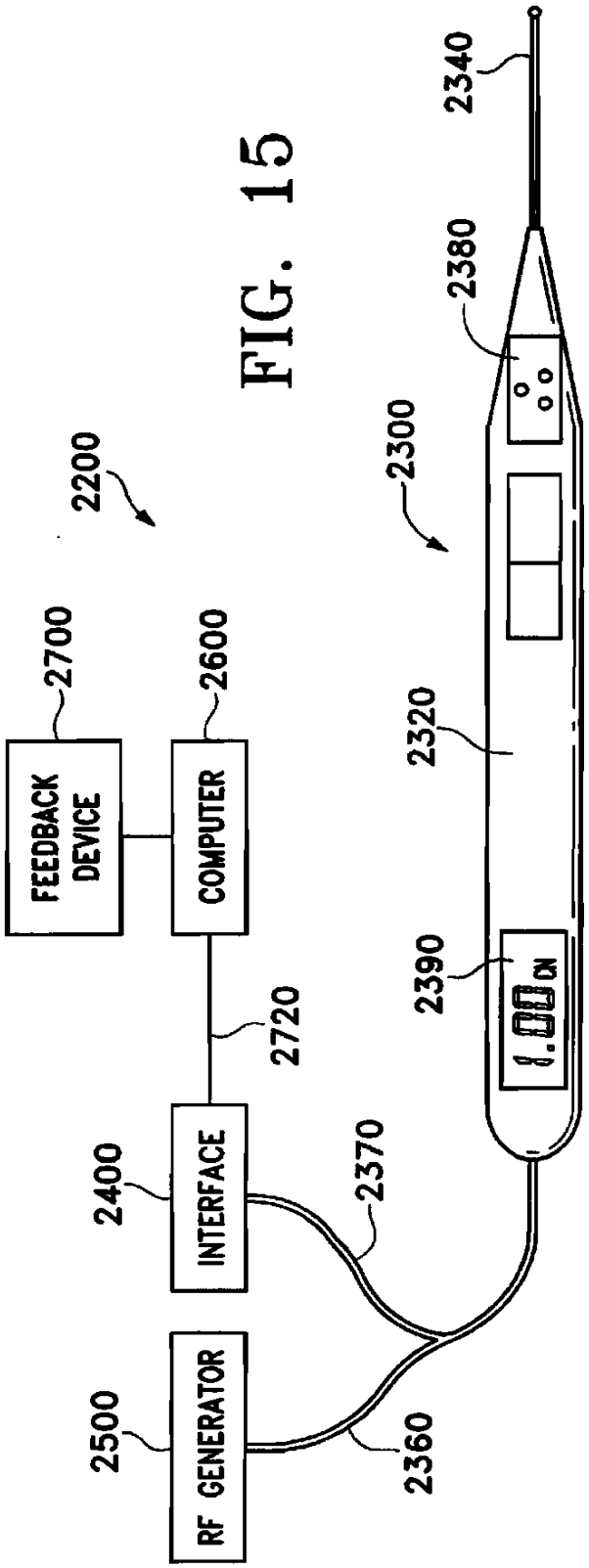


FIG. 15

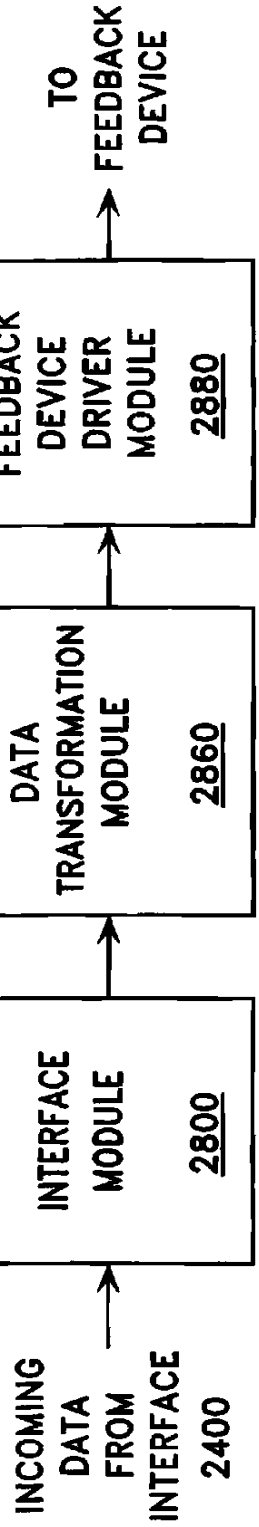


FIG. 16

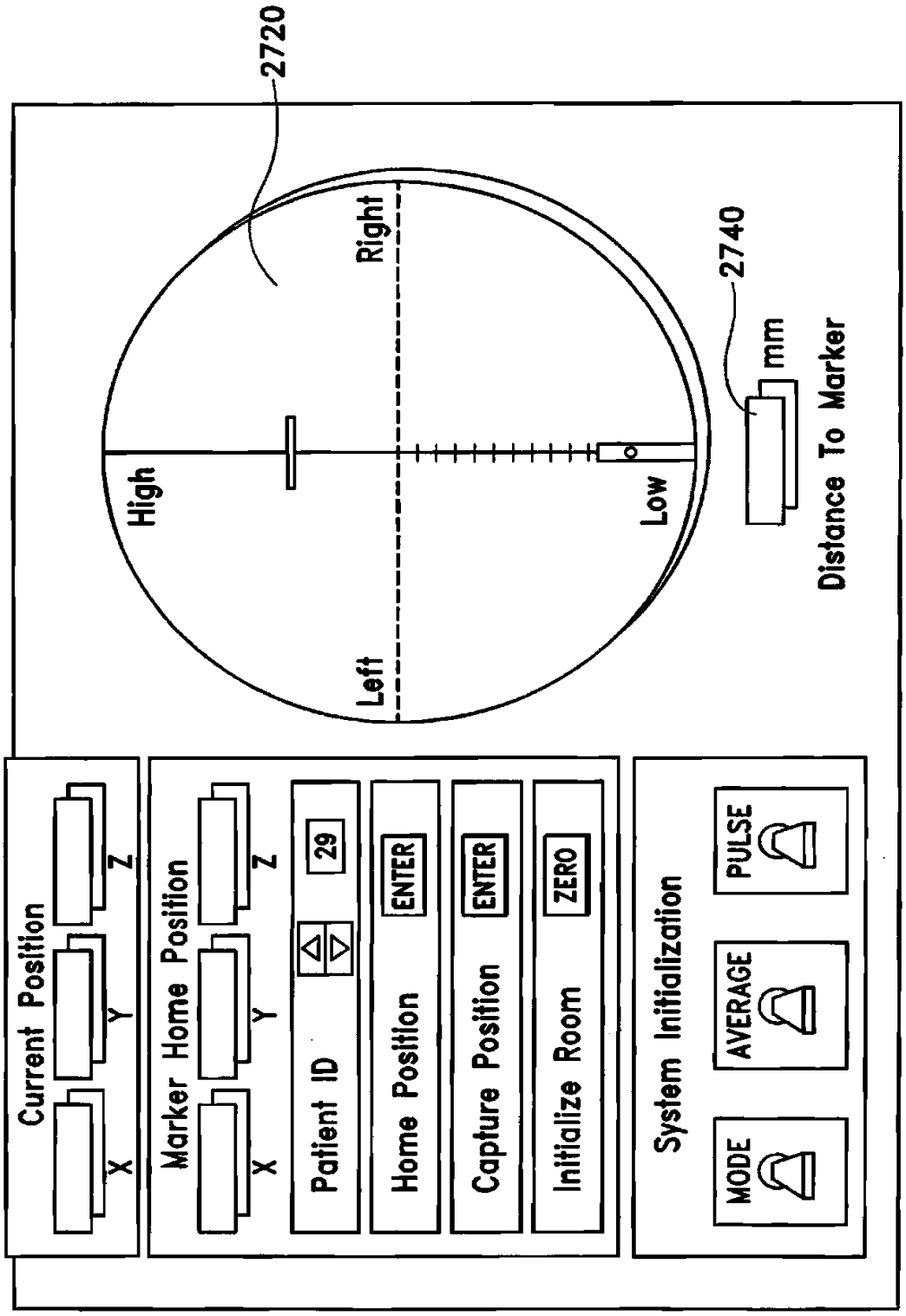


Fig. 17

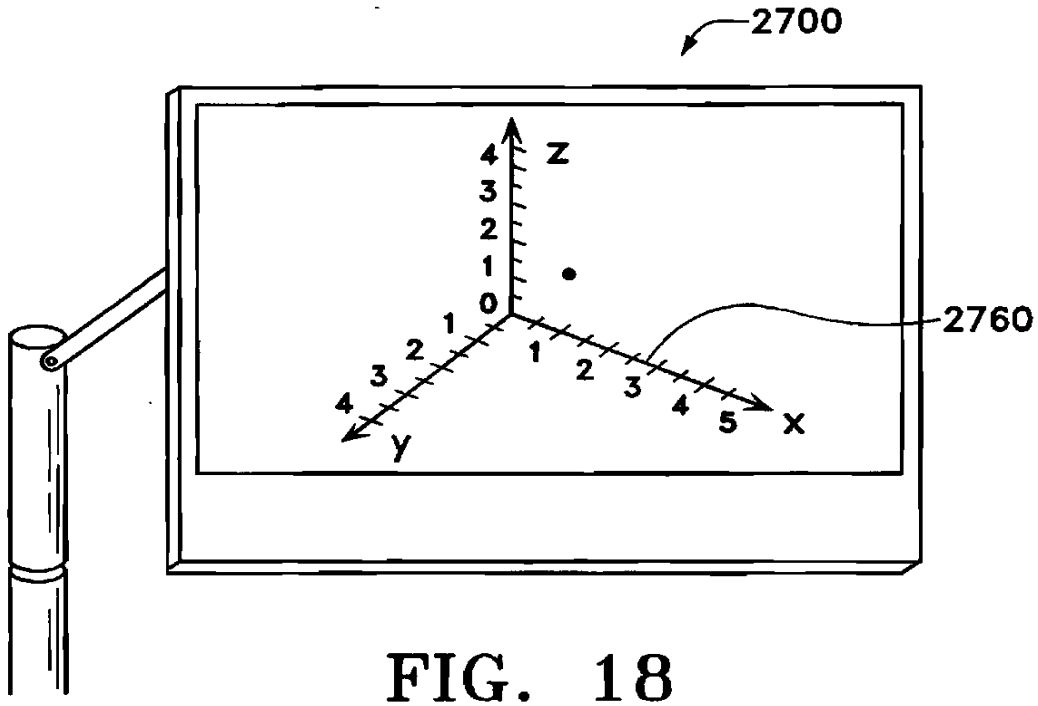


FIG. 18

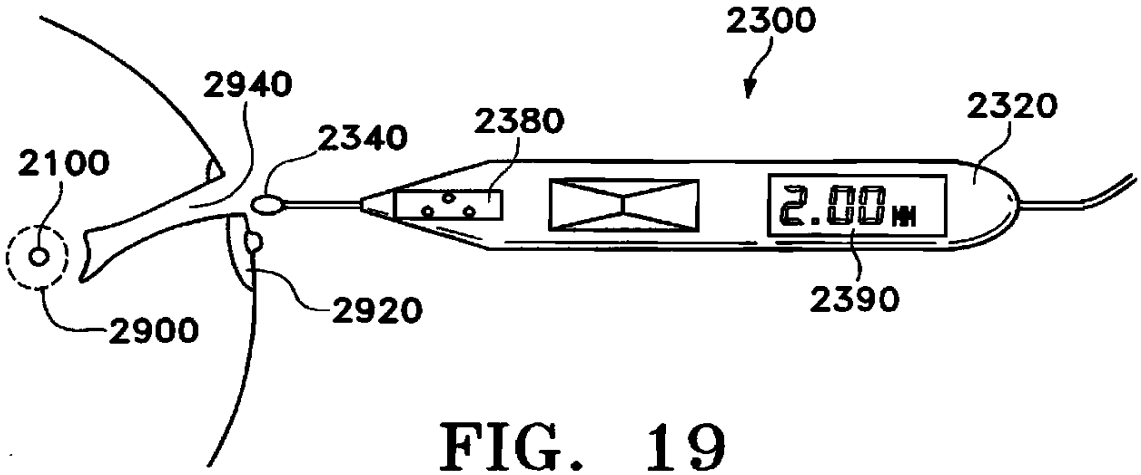


FIG. 19

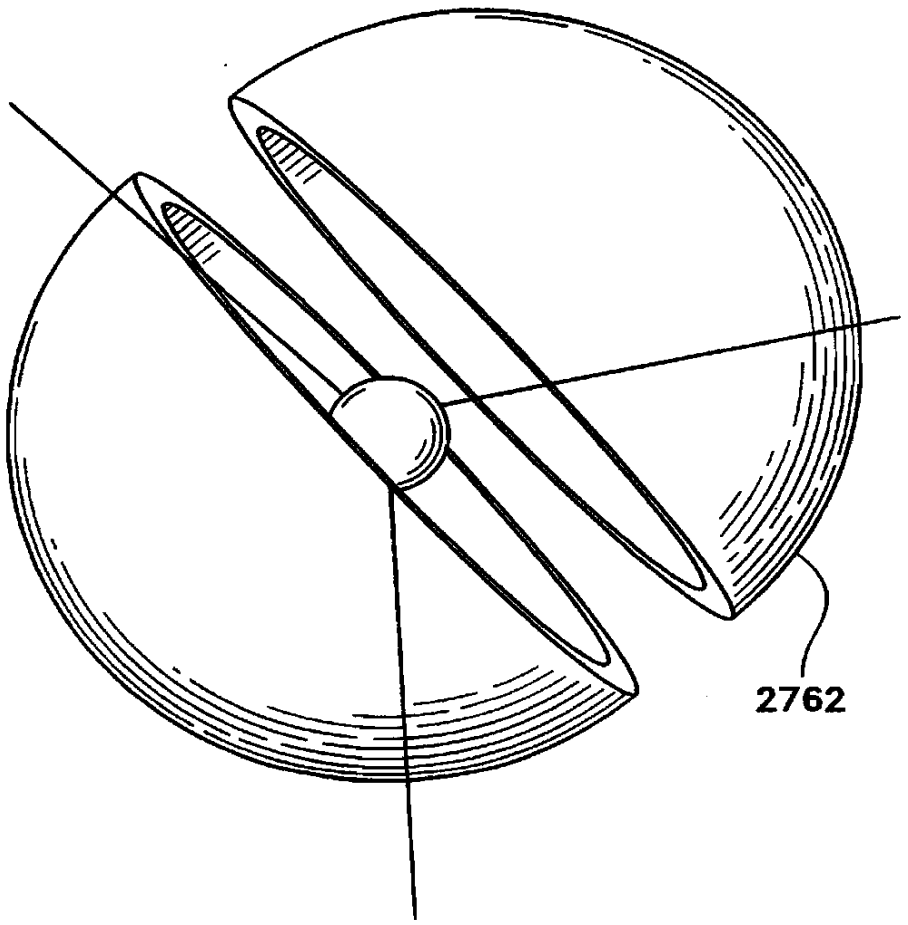


FIG. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18394

A. **CLASSIFICATION OF SUBJECT MATTER**
IPC(7) :A61B 18/18
US CL :606/002
According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/002

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,460,182 A (GOODMAN et al.) 24 October 1995, entire document.	1-46
Y	US 5,409,004 A (SLOAN) 25 April 1995, entire document.	1-42
Y	US,5,382,251 A(HOOD et al.) 17 January 1995, entire document.	1-34
Y	US 5,720,772 A (ECKHOUSE) 24 February 1998, entire document.	43-46
Y	US 5,403,306 A (EDWARDS et al.) 04 April 1995, entire document.	47-70
Y	US 5,709,676 A (ALT) 20 January. 1998, entire document.	50-66

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 AUGUST 2000	Date of mailing of the international search report 03 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer AHMED M. FARAH Telephone No. (703) 308- 3549

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/18394

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,628,744 A (COLEMAN et al.) 13 May 1997, entire document.	53-70
Y	US 5,059,197 A (URIE et al.) 22 October 1991, entire document.	67-70
Y	US 4,944,308 A (AKERFELDT) 31 July 1990, entire document.	1-34, 67-70

Form PCT/ISA/210 (continuation of second sheet) (July 1998)*